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(54) Title: NOVEL HCV NON-STRUCTURAL POLYPEPTIDE

(57) Abstract: Polypeptides comprising a mutant non-structural Hepatitis C virus useful in diagnostic and/or immunogenic compositions are disclosed, in which the mutant is an N-terminal mutation that functionally disrupt the catalytic domain of NS3. Polynucleotides encoding these polypeptides, host cells transformed with polynucleotides and methods of using the polypeptides and polynucleotides are also disclosed.

5                                    **NOVEL HCV NON-STRUCTURAL POLYPEPTIDE**

**FIELD OF THE INVENTION**

10            The present invention relates to polypeptides comprising a mutant non-structural Hepatitis C virus ("HCV") polypeptide useful for immunogenic compounds for use against HCV, methods of preparing and using the same, and immunogenic compositions comprising the same. The present invention also relates to compositions comprising (a) a mutant non-structural HCV polypeptide and (b) a viral polypeptide that is not a non-structural HCV polypeptide and methods of using these compositions.

15

**BACKGROUND OF THE INVENTION**

HCV is now recognized as the major agent of chronic hepatitis and liver disease worldwide. It is estimated that HCV infects about 400 million people worldwide, corresponding to more than 3% of the world population.

20            Hepatitis C virus ("HCV") is a small enveloped RNA *flavivirus*, which contains a positive-stranded RNA genome of about 10 kilobases. The genome has a single uninterrupted ORF that encodes a protein of 3010-3011 amino acids. The structural proteins of HCV include a core protein (C), which is highly immunogenic, as well as two envelope proteins (E1 and E2), which likely form a heterodimer *in vivo*, and non-structural proteins NS2-NS5. It is known that the NS3 region of the virus is important for post-translational processing of the polyprotein into individual proteins, and the NS5 region encodes an RNA-dependant RNA polymerase.

25            Virus-specific T lymphocytes, along with neutralizing antibodies, are the mainstay of the antiviral immune defense in established viral infections. Whereas CD8<sup>+</sup> cytotoxic T cells eliminate virus-infected-cells, CD4<sup>+</sup> T helper cells are essential for the efficient regulation of the antiviral immune response. CD4<sup>+</sup> T helper cells recognize specific antigens as peptides bound to autologous HLA class II molecules (viral antigens or particles are taken up by professional antigen-presenting cells, processed to peptides, bound to HLA class II molecules in the lysosomal compartment,

30

and transported back to the cell surface). Several observations support an important role of CD4<sup>+</sup> T cells in the elimination of HCV infection. Tsai *et al.*, 1997 Hepatology 25:449-458; Diepolder *et al* 1995 Lancet 346: 1—6-1009; Missale *et al* 1996 JCI 98: 706-714; Botarelli *et al* 1993; Gastro 104: 580-587; Diepolder *et al* 1997 J.Virol 71: 6011. Immunogenic peptides usually have a minimal length of 8-11 amino acids. However, since the peptide binding groove of HLA class II molecules seems to be open at both ends, longer peptides are tolerated. Thus peptides eluted from HLA class II molecules are typically in the range of 15-25 amino acids. HLA class II molecules are extremely polymorphic and each allele seems to have its individual requirements for peptide binding. Thus the HLA class II repertoire of a given individual determines which viral peptides can be presented to T cells. Recognition of the specific HLA-peptide complex by the T cell receptor accompanied by appropriate costimulatory signals lead to T cell activation, secretion of cytokines, and T cell proliferation.

Numerous studies demonstrate that HLA Class II restricted CD4<sup>+</sup> responses are determined by stimulating peripheral blood mononuclear cells with recombinant viral antigens or peptides. Botarelli *et al.*, (1993) Gastroenterology 104:580-587; Ferrari *et al.*, (1994) Hepatology 19:286-295; Minutello *et al.*, (1993) C. J. Exp. Med. 178:17-25; Hoffmann *et al.*, (1995) Hepatology 21:632-638; Iwata *et al.*, (1995) Hepatology 22:1057-1064; and Tsai *et al.*, (1995) Hepatology 21:908-912.

Polyclonal multispecific CD8<sup>+</sup> T cell responses have been detected in patients with chronic hepatitis C. Additionally, CD8<sup>+</sup> CTL's were shown to be important in resolving acute HCV infection in chimpanzees (Cooper *et al.*, Immunity 1999). About 50% of patients with chronic hepatitis C demonstrate a detectable virus-specific CD4<sup>+</sup> T cell response, which is most frequently directed against HCV core and/or NS4 and tends to be more common in patients who achieve sustained viral clearance during interferon- $\alpha$  therapy.

Depending on the pattern of lymphokines, CD4<sup>+</sup> T helper cells have been classified as TH1, TH0, or TH2. Cytokines of the TH1 type are typically IFN- $\gamma$ , lymphotoxin, and interleukin-2 (IL-2), which are believed to support activation of virus-specific CD8<sup>+</sup> T cells and natural killer cells. The TH2 cytokines IL-4, IL-5, IL-10, and IL-13 are important for B cell activation and differentiation, thus inducing a humoral immune response.

During acute hepatitis C infection a strong and sustained TH1/TH0 response to NS3 and possibly to other nonstructural proteins is associated with a self-limited course of the disease. Diapolder *et al.*, (1995) Lancet 346:1006-1007, showed all CD4<sup>+</sup> T cell clones to have a TH1 or TH0 cytokine profile, suggesting that the clones support cytotoxic immune mechanisms *in vivo*. The majority of CD4<sup>+</sup> T cell clones responded to a relatively short segment of NS3, namely amino acids 1207-1278, suggesting that this region of NS3 is immunodominant for CD4<sup>+</sup> T cells. More than 70% of those who contract HCV develop chronic infection and hepatitis, and a significant portion of them progress to cirrhosis and eventually hepatocellular carcinoma. The only approved therapy at present is a 6- to 12- month course of interferon  $\alpha$ , which leads to sustained improvement in only 20% of patients. So far, no commercial vaccine is available.

Thus, there remains a need for compositions and methods capable of promoting anti-HCV responses.

## 15 SUMMARY OF THE INVENTION

In one aspect, the present invention relates to isolated polypeptides comprising mutant hepatitis C ("HCV") polypeptides comprising at least portions of NS3, NS4, and NS5. In a preferred aspect, NS3 is encoded by a nucleic acid sequence having an N-terminal deletion to remove the catalytic domain. The NS mutant polypeptides can include NS3, NS4s, NS4b, NS5a, NS5b or portions thereof. For example, in various embodiments, the mutant NS polypeptide comprises NS3, NS4 (NS4a and NS4b) and NS5 (NS5a and NS5b). In other embodiments, the NS polypeptide consists of NS3 and NS4 (for example, NS4a and/or NS4b) or NS3 and NS5 (for example, NS5a and/or NS5b). Other combinations of full-length or fragments of non-structural components are also contemplated.

In another preferred aspect, the polypeptides further comprise a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, and include, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV.



Thus, the invention includes an isolated mutant non-structural ("NS") HCV polypeptide comprising a polypeptide having a mutation in the catalytic domain of NS3 that functionally disrupts the catalytic domain. The mutation can be, for example, a deletion or a substitution mutation. In certain embodiments, the mutant NS polypeptide comprises NS3, NS4 and NS5. In other embodiments, the mutant NS polypeptides described herein further comprise a second viral polypeptide that is not NS3, NS4, or NS5 of HCV, for example an HCV Core polypeptide ("C"), or fragment thereof, or an HCV envelope protein ("E"), for example E1 and/or E2. In certain embodiments, C is truncated (*e.g.*, at amino acid 121).

10 In another aspect, the present invention relates to compositions comprising any of the mutant hepatitis C ("HCV") polypeptides described herein, for example polypeptides comprising at least portions of NS3, NS4, and NS5. In a preferred aspect, NS3 is encoded by a nucleic acid sequence having an N-terminal deletion to disrupt the function of the catalytic domain, for example by removing this domain. In another preferred aspect, the polypeptides further comprise a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, and include, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV. In another aspect, the invention includes a composition comprising (a) any of the polypeptides described herein; and (b) a pharmaceutically acceptable excipient (*e.g.*, carrier and/or adjuvant).

25 In another aspect, the invention includes an isolated and purified polynucleotide which encodes any of the mutant HCV polypeptides described herein. In certain embodiments, the invention includes a composition comprising (a) the isolated purified polynucleotide encoding any of the mutant HCV polypeptides; and (b) a pharmaceutically acceptable excipient. The polynucleotide, can be for example, DNA in a plasmid, or is in a plasmid. Additionally, the polynucleotides described herein may be included in an expression vector as shown in the attached Figures and Sequence Listings.

In another aspect, the present invention relates to host cells transformed with expression vectors comprising a nucleic acid sequence encoding a mutant HCV polypeptide comprising at least portions of NS3, NS4, and NS5. In a preferred aspect, the expression vectors of the host cells further comprises at least one nucleic acid  
5 sequence encoding a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, and include, for example, truncated or otherwise mutant  
10 HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV. In another preferred aspect the nucleic acid sequences of the expression vectors are coexpressed. In yet another preferred aspect, the host cells are yeast cells or mammalian cells.

In another aspect, the present invention relates to expression vectors comprising  
15 a nucleic acid sequence encoding a mutant HCV polypeptide comprising NS3, NS4, and NS5. In a preferred aspect, the expression vectors of the host cells further comprises at least one nucleic acid sequence encoding a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are  
20 preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Importantly, such polypeptides need not be encoded by a natural HCV genome, such as, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV. In another aspect, the present invention relates to methods of preparing a mutant HCV  
25 polypeptides. In a preferred aspect, the method comprises the steps of transforming a host cell with an expression vector, said vector comprising a nucleic acid sequence encoding a mutant HCV polypeptide comprising at least portions of NS3, NS4, and NS5, and isolating said polypeptide. In another preferred aspect the HCV polypeptide further comprises a viral polypeptide that is not a non-structural HCV polypeptide.  
30 Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by

a natural HCV genome, and include, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV. In another preferred aspect the host cells are yeast cells or mammalian cells.

5           In another aspect, the present invention relates to antibodies which specifically bind to mutant HCV polypeptide comprising NS3, NS4, and NS5, and to methods of making and using the same. In a preferred aspect, the HCV polypeptide further comprises a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, such as, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, and include, for example, polypeptides of HBV. In another preferred aspect, the antibody is either monoclonal or polyclonal.

15           In yet another aspect, a method of preparing a mutant NS HCV polypeptide, wherein the method comprises the steps of (a) transforming a host cell with any of the expression vectors described herein, under conditions wherein the polypeptide is expressed; and (b) isolating the polypeptide. The host cell can be, for example, a yeast cell, a mammalian cell a plant cell or an insect cell. The polypeptide can be expressed and isolated intracellularly or can be secreted and isolated from the surrounding environment.

20           In a still further aspect, a method of eliciting an immune response in a subject is provided. The immune response can be elicited by administering any of the polynucleotides and/or polypeptides described herein in one or multiple doses.

25           These and other embodiments of the subject invention will readily occur to those of skill in the art in light of the disclosure herein.

#### **BRIEF DESCRIPTION OF THE FIGURES**

30           FIG. 1 shows the cloning scheme for generating pCMV-NS35.  
FIG. 2 shows the 9621bp vector pCMV-NS35.

FIG. 3 shows the nucleic acid sequence of pCMV-NS35 (SEQ ID NO:1), including the nucleic acid sequence of the NS35 ORF, and also the translation of NS35 (SEQ ID NO:2).

FIG. 4 shows the 9621bp pCMV-delNS35.

- 5 FIG. 5 shows the nucleic acid sequence of pCMV-delNS35 (SEQ ID NO:3), including the nucleic acid sequence of the delNS35 ORF, and also the translation of the delNS35 polypeptide (SEQ ID NO:4).

FIG. 6 shows the 4276bp pCMV-II.

FIG. 7 shows the nucleic acid sequence of pCMV-II (SEQ ID NO:5).

- 10 FIG. 8 shows the 6300bp pCMV-NS34A.

FIG. 9 shows the nucleic acid sequence of pCMV-NS34A (SEQ ID NO:6), including the nucleic acid sequence of the NS34A ORF, and also the translation of NS34A (SEQ ID NO:7).

FIG. 10 shows the cloning scheme for generating pd.ΔNS3NS5.

- 15 FIG. 11 shows the nucleic and amino acid sequences of pd.ΔNS3NS5 (SEQ ID NO:8 and 9).

FIG. 12 shows the Western blot of proteins expressed by *S. cerevisiae* strain AD3 transformed with pd.ΔNS3NS5.

FIG. 13 shows the cloning scheme for generating pd.ΔNS3NS5.pj.

- 20 FIG. 14 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj (SEQ ID NO:10 and 11).

FIG. 15 shows the Western blot of proteins expressed by *S. cerevisiae* strain AD3 transformed with pd.ΔNS3NS5.pj, specifically demonstrating the expression of ΔNS3NS5 polypeptide.

- 25 FIG. 16 shows the cloning scheme for generating pdΔNS3NS5.pj.core121RT and pdΔNS3NS5.pj.core173RT.

FIG. 17 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj.core121 (SEQ ID NO:12 and 13).

- 30 FIG. 18 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj.core173 (SEQ ID NO:14 and 15).

FIG. 19 shows the Western blot of proteins expressed by *S. cerevisiae* strain AD3 transformed with pd.ΔNS3NS5.pj, specifically demonstrating the expression of

$\Delta$ NS3NS5.core121 and  $\Delta$ NS3NS5.core173 polypeptides. Lanes 1 and 7 show See Blue Standards. Lane 2 shows control yeast plasmid. Lanes 3 and 4 show  $\Delta$ NS3NS5.core121RT polypeptide, colonies 1 and 2. Lanes 5 and 6 show  $\Delta$ NS3NS5.core173RT polypeptide, colonies 3 and 4.

5 FIG. 20 shows the cloning scheme for generating pd $\Delta$ NS3NS5.pj.core140RT and pd $\Delta$ NS3NS5.pj.core150RT.

FIG. 21 shows the nucleic and amino acid sequences of pd. $\Delta$ NS3NS5.pj.core140 (SEQ ID NO:16 and 17).

10 FIG. 22 shows the nucleic and amino acid sequences of pd. $\Delta$ NS3NS5.pj.core150 (SEQ ID NO:18 and 19).

FIG. 23 shows the Western blot of proteins expressed by *S. cerevisiae* strain AD3 transformed with pd. $\Delta$ NS3NS5.pj, specifically demonstrating the expression of  $\Delta$ NS3NS5core140 and  $\Delta$ NS3NS5core150 polypeptides. Lane 1 shows See Blue Standards. Lanes 2 and 3 show  $\Delta$ NS3NS5core140RT polypeptide, colonies 5 and 6.

15 Lanes 4 and 5 show  $\Delta$ NS3NS5core150RT polypeptide, colonies 7 and 8. Lane 6 shows control yeast plasmid. Lane 7 shows  $\Delta$ NS3NS5core121RT polypeptide, colony 1. Lane 8 shows  $\Delta$ NS3NS5core173RT polypeptide, colony 5.

#### DETAILED DESCRIPTION OF THE INVENTION

20 The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology, microbiology, recombinant DNA techniques, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See e.g., Sambrook, et al., MOLECULAR CLONING; A LABORATORY MANUAL (1989); DNA CLONING, VOLUMES I AND II (D. N. Glover ed. 1985); OLIGONUCLEOTIDE SYNTHESIS (M. J. Gait ed., 1984);  
25 NUCLEIC ACID HYBRIDIZATION (B. D. Hames & S. J. Higgins eds. 1984); TRANSCRIPTION AND TRANSLATION (B. D. Hames & S. J. Higgins eds. 1984); ANIMAL CELL CULTURE (R. I. Freshney ed. 1986); IMMOBILIZED CELLS AND ENZYMES (IRL Press, 1986); B. Perbal, A PRACTICAL GUIDE TO MOLECULAR  
30 CLONING (1984); the series, METHODS OF ENZYMOLOGY (Academic Press, Inc.); GENE TRANSFER VECTORS FOR MAMMALIAN CELLS (J. H. Miller and M. P. Calos eds. 1987, Cold Springs Harbor Laboratory), Methods in Enzymology Vol.

154 and Vol. 155 (Wu and Grossman, and Wu, eds., respectively); Mayer and Walker  
eds. (1987), IMMUNOHISTOCHEMICAL METHODS IN CELL AND  
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PURIFICATION: PRINCIPALS AND PRACTICE, Second Edition (Springer-Verlag,  
5 New York); and HANDBOOK OF EXPERIMENTAL IMMUNOLOGY, VOLUMES  
I-IV (D. M. Weir and C. C. Blackwell eds. 1986).

It must be noted that, as used in this specification and the appended claims, the  
singular forms "a", "an" and "the" include plural referents unless the content clearly  
dictates otherwise. Thus, for example, reference to "an antigen" includes a mixture of  
10 two or more antigens, and the like.

### I. Definitions

In describing the present invention, the following terms will be employed, and  
are intended to be defined as indicated below.

15 The term "hepatitis C virus" (HCV) refers to an agent causative of Non-A, Non-  
B Hepatitis (NANBH). The nucleic acid sequence and putative amino acid sequence of  
HCV is described in U.S. Patent Nos. 5,856,437 and 5,350,671. The disease caused by  
HCV is called hepatitis C, formerly called NANBH. The term HCV, as used herein,  
denotes a viral species of which pathenogenic strains cause NANBH, as well as  
20 attenuated strains or defective interfering particles derived therefrom.

HCV is a member of the viral family flaviviridae. The morphology and  
composition of Flavivirus particles are known, and are discussed in Reed et al., *Curr.*  
*Stud. Hematol. Blood Transfus.* (1998), 62:1-37; HEPATITIS C VIRUSES IN FIELDS  
VIROLOGY (B.N. Fields, D.M. Knipe, P.M. Howley, eds.) (3d ed. 1996). It has  
25 recently been found that portions of the HCV genome are also homologous to  
pestiviruses. Generally, with respect to morphology, Flaviviruses contain a central  
nucleocapsid surrounded by a lipid bilayer. Virions are spherical and have a diameter  
of about 40-50 nm. Their cores are about 25-30 nm in diameter. Along the outer  
surface of the virion envelope are projections that are about 5-10 nm long with terminal  
30 knobs about 2 nm in diameter.

The HCV genome is comprised of RNA. It is known that RNA containing  
viruses have relatively high rates of spontaneous mutation. Therefore, there can be

multiple strains, which can be virulent or avirulent, within the HCV class or species. The ORF of HCV, including the translation spans of the core, non-structural, and envelope proteins, is shown in U.S. Patent Nos. 5,856,437 and 5,350,671.

The terms "polypeptide" and "protein" refer to a polymer of amino acid residues and are not limited to a minimum length of the product. Thus, peptides, oligopeptides, dimers, multimers, and the like, are included within the definition. Both full-length proteins and fragments thereof are encompassed by the definition. The terms also include postexpression modifications of the polypeptide, for example, glycosylation, acetylation, phosphorylation and the like. Furthermore, for purposes of the present invention, a "polypeptide" refers to a protein which includes modifications, such as deletions, additions and substitutions (generally conservative in nature), to the native sequence, so long as the protein maintains the desired activity. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through mutations of hosts which produce the proteins or errors due to PCR amplification.

An HCV polypeptide is a polypeptide, as defined above, derived from the HCV polyprotein. The polypeptide need not be physically derived from HCV, but may be synthetically or recombinantly produced. Moreover, the polypeptide may be derived from any of the various HCV strains, such as from strains 1, 2, 3 or 4 of HCV. A number of conserved and variable regions are known between these strains and, in general, the amino acid sequences of epitopes derived from these regions will have a high degree of sequence homology, e.g., amino acid sequence homology of more than 30%, preferably more than 40%, when the two sequences are aligned and homology determined by any of the programs or algorithms described herein. Thus, for example, the term "NS4" polypeptide refers to native NS4 from any of the various HCV strains, as well as NS4 analogs, muteins and immunogenic fragments, as defined further below.

Further, the terms "ΔNS35," "delNS35," "ΔNS3NS5," and "ΔNS3-5" as used herein refer to a mutant polypeptide, comprising at least portions of NS3, NS4, or NS5, comprising a deletion in, or mutation of, the NS3 protease active site region to render the protease non-functional. In one embodiment, ΔNS3-5 comprises amino acids 1242-3011, as shown in FIG. 5, or polypeptides substantially homologous thereto. It will be readily apparent to one of ordinary skill in the art how to determine that NS3 protease

has been rendered non-functional. If the protease is functional, one will obtain protein of the expected molecular weight upon expression. As set forth in Example 2 and Figure 15, using SDS-page, 4-20%, a protein having a molecular weight of approximately 194kD was obtained when strain AD3 was transformed with  
5 pd.ΔNS3NS5.PJ clone #5. One skilled in the art could readily determine whether a protein of the desired molecular weight was expressed for any given deletion or mutation.

The terms "analog" and "mutein" refer to biologically active derivatives of the reference molecule, or fragments of such derivatives, that retain desired activity, such  
10 as the ability to stimulate a cell-mediated immune response, as defined below. In general, the term "analog" refers to compounds having a native polypeptide sequence and structure with one or more amino acid additions, substitutions (generally conservative in nature) and/or deletions, relative to the native molecule, so long as the modifications do not destroy immunogenic activity. The term "mutein" refers to  
15 peptides having one or more peptide mimics ("peptoids"), such as those described in International Publication No. WO 91/04282. Preferably, the analog or mutein has at least the same immunoactivity as the native molecule. Methods for making polypeptide analogs and muteins are known in the art and are described further below.

Particularly preferred analogs include substitutions that are conservative in  
20 nature, i.e., those substitutions that take place within a family of amino acids that are related in their side chains. Specifically, amino acids are generally divided into four families: (1) acidic -- aspartate and glutamate; (2) basic -- lysine, arginine, histidine; (3) non-polar -- alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and (4) uncharged polar -- glycine, asparagine, glutamine, cysteine, serine  
25 threonine, tyrosine. Phenylalanine, tryptophan, and tyrosine are sometimes classified as aromatic amino acids. For example, it is reasonably predictable that an isolated replacement of leucine with isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar conservative replacement of an amino acid with a structurally related amino acid, will not have a major effect on the biological activity.  
30 For example, the polypeptide of interest may include up to about 5-10 conservative or non-conservative amino acid substitutions, or even up to about 15-25 conservative or non-conservative amino acid substitutions, or any integer between 5-25, so long as the



desired function of the molecule remains intact. One of skill in the art may readily determine regions of the molecule of interest that can tolerate change by reference to Hopp/Woods and Kyte-Doolittle plots, well known in the art.

By "fragment" is intended a polypeptide consisting of only a part of the intact  
5 full-length polypeptide sequence and structure. The fragment can include a C-terminal deletion and/or an N-terminal deletion of the native polypeptide. An "immunogenic fragment" of a particular HCV protein will generally include at least about 5-10 contiguous amino acid residues of the full-length molecule, preferably at least about 15-25 contiguous amino acid residues of the full-length molecule, and most preferably  
10 at least about 20-50 or more contiguous amino acid residues of the full-length molecule, that define an epitope, or any integer between 5 amino acids and the full-length sequence, provided that the fragment in question retains immunogenic activity, as measured by the assays described herein. For a description of various HCV epitopes, see, e.g., Chien et al., *Proc. Natl. Acad. Sci. USA* (1992) 89:10011-10015;  
15 Chien et al., *J. Gastroent. Hepatol.* (1993) 8:S33-39; Chien et al., International Publication No. WO 93/00365; Chien, D.Y., International Publication No. WO 94/01778; commonly owned, allowed U.S. Patent Application Serial Nos. 08/403,590 and 08/444,818.

The term "epitope" as used herein refers to a sequence of at least about 3 to 5,  
20 preferably about 5 to 10 or 15, and not more than about 1,000 amino acids (or any integer therebetween), which define a sequence that by itself or as part of a larger sequence, binds to an antibody generated in response to such sequence. There is no critical upper limit to the length of the fragment, which may comprise nearly the full-length of the protein sequence, or even a fusion protein comprising two or more  
25 epitopes from the HCV polyprotein. An epitope for use in the subject invention is not limited to a polypeptide having the exact sequence of the portion of the parent protein from which it is derived. Indeed, viral genomes are in a state of constant flux and contain several variable domains which exhibit relatively high degrees of variability between isolates. Thus the term "epitope" encompasses sequences identical to the  
30 native sequence, as well as modifications to the native sequence, such as deletions, additions and substitutions (generally conservative in nature).

Regions of a given polypeptide that include an epitope can be identified using any number of epitope mapping techniques, well known in the art. See, e.g., *Epitope Mapping Protocols* in *Methods in Molecular Biology*, Vol. 66 (Glenn E. Morris, Ed., 1996) Humana Press, Totowa, New Jersey. For example, linear epitopes may be  
5 determined by e.g., concurrently synthesizing large numbers of peptides on solid supports, the peptides corresponding to portions of the protein molecule, and reacting the peptides with antibodies while the peptides are still attached to the supports. Such techniques are known in the art and described in, e.g., U.S. Patent No. 4,708,871; Geysen et al. (1984) *Proc. Natl. Acad. Sci. USA* 81:3998-4002; Geysen et al. (1986)  
10 *Molec. Immunol.* 23:709-715. Similarly, conformational epitopes are readily identified by determining spatial conformation of amino acids such as by, e.g., x-ray crystallography and 2-dimensional nuclear magnetic resonance. See, e.g., *Epitope Mapping Protocols, supra*. Antigenic regions of proteins can also be identified using standard antigenicity and hydropathy plots, such as those calculated using, e.g., the  
15 Omega version 1.0 software program available from the Oxford Molecular Group. This computer program employs the Hopp/Woods method, Hopp et al., *Proc. Natl. Acad. Sci USA* (1981) 78:3824-3828 for determining antigenicity profiles, and the Kyte-Doolittle technique, Kyte et al., *J. Mol. Biol.* (1982) 157:105-132 for hydropathy plots.

As used herein, the term "conformational epitope" refers to a portion of a full-  
20 length protein, or an analog or mutein thereof, having structural features native to the amino acid sequence encoding the epitope within the full-length natural protein. Native structural features include, but are not limited to, glycosylation and three dimensional structure. Preferably, a conformational epitope is produced recombinantly and is expressed in a cell from which it is extractable under conditions which preserve its  
25 desired structural features, e.g. without denaturation of the epitope. Such cells include bacteria, yeast, insect, and mammalian cells. Expression and isolation of recombinant conformational epitopes from the HCV polyprotein are described in e.g., International Publication Nos. WO 96/04301, WO 94/01778, WO 95/33053, WO 92/08734.

An "immunological response" to an HCV antigen (including both polypeptide  
30 and polynucleotides encoding polypeptides that are expressed *in vivo*) or composition is the development in a subject of a humoral and/or a cellular immune response to molecules present in the composition of interest. For purposes of the present invention,

a "humoral immune response" refers to an immune response mediated by antibody molecules, while a "cellular immune response" is one mediated by T-lymphocytes and/or other white blood cells. One important aspect of cellular immunity involves an antigen-specific response by cytolytic T-cells ("CTLs"). CTLs have specificity for peptide antigens that are presented in association with proteins encoded by the major histocompatibility complex (MHC) and expressed on the surfaces of cells. CTLs help induce and promote the intracellular destruction of intracellular microbes, or the lysis of cells infected with such microbes. Another aspect of cellular immunity involves an antigen-specific response by helper T-cells. Helper T-cells act to help stimulate the function, and focus the activity of, nonspecific effector cells against cells displaying peptide antigens in association with MHC molecules on their surface. A "cellular immune response" also refers to the production of cytokines, chemokines and other such molecules produced by activated T-cells and/or other white blood cells, including those derived from CD4+ and CD8+ T-cells.

A composition or vaccine that elicits a cellular immune response may serve to sensitize a vertebrate subject by the presentation of antigen in association with MHC molecules at the cell surface. The cell-mediated immune response is directed at, or near, cells presenting antigen at their surface. In addition, antigen-specific T-lymphocytes can be generated to allow for the future protection of an immunized host.

The ability of a particular antigen to stimulate a cell-mediated immunological response may be determined by a number of assays, such as by lymphoproliferation (lymphocyte activation) assays, CTL cytotoxic cell assays, or by assaying for T-lymphocytes specific for the antigen in a sensitized subject. Such assays are well known in the art. See, e.g., Erickson et al., *J. Immunol.* (1993) 151:4189-4199; Doe et al., *Eur. J. Immunol.* (1994) 24:2369-2376; and the examples below.

Thus, an immunological response as used herein may be one which stimulates the production of CTLs, and/or the production or activation of helper T- cells. The antigen of interest may also elicit an antibody-mediated immune response. Hence, an immunological response may include one or more of the following effects: the production of antibodies by B-cells; and/or the activation of suppressor T-cells and/or  $\gamma\delta$  T-cells directed specifically to an antigen or antigens present in the composition or vaccine of interest. These responses may serve to neutralize infectivity, and/or mediate

antibody-complement, or antibody dependent cell cytotoxicity (ADCC) to provide protection or alleviation of symptoms to an immunized host. Such responses can be determined using standard immunoassays and neutralization assays, well known in the art.

5           A "coding sequence" or a sequence which "encodes" a selected polypeptide, is a nucleic acid molecule which is transcribed (in the case of DNA) and translated (in the case of mRNA) into a polypeptide *in vitro* or *in vivo* when placed under the control of appropriate regulatory sequences. The boundaries of the coding sequence are determined by a start codon at the 5' (amino) terminus and a translation stop codon at  
10       the 3' (carboxy) terminus. A transcription termination sequence may be located 3' to the coding sequence.

          A "nucleic acid" molecule or "polynucleotide" can include both double- and single-stranded sequences and refers to, but is not limited to, cDNA from viral, procaryotic or eucaryotic mRNA, genomic DNA sequences from viral (e.g. DNA  
15       viruses and retroviruses) or procaryotic DNA, and especially synthetic DNA sequences. The term also captures sequences that include any of the known base analogs of DNA and RNA.

          "Operably linked" refers to an arrangement of elements wherein the components so described are configured so as to perform their desired function. Thus,  
20       a given promoter operably linked to a coding sequence is capable of effecting the expression of the coding sequence when the proper transcription factors, etc., are present. The promoter need not be contiguous with the coding sequence, so long as it functions to direct the expression thereof. Thus, for example, intervening untranslated yet transcribed sequences can be present between the promoter sequence and the coding  
25       sequence, as can transcribed introns, and the promoter sequence can still be considered "operably linked" to the coding sequence.

          "Recombinant" as used herein to describe a nucleic acid molecule means a polynucleotide of genomic, cDNA, viral, semisynthetic, or synthetic origin which, by virtue of its origin or manipulation is not associated with all or a portion of the  
30       polynucleotide with which it is associated in nature. The term "recombinant" as used with respect to a protein or polypeptide means a polypeptide produced by expression of a recombinant polynucleotide. In general, the gene of interest is cloned and then

expressed in transformed organisms, as described further below. The host organism expresses the foreign gene to produce the protein under expression conditions.

A "control element" refers to a polynucleotide sequence which aids in the expression of a coding sequence to which it is linked. The term includes promoters, transcription termination sequences, upstream regulatory domains, polyadenylation  
5 signals, untranslated regions, including 5'-UTRs and 3'-UTRs and when appropriate, leader sequences and enhancers, which collectively provide for the transcription and translation of a coding sequence in a host cell.

A "promoter" as used herein is a DNA regulatory region capable of binding  
10 RNA polymerase in a host cell and initiating transcription of a downstream (3' direction) coding sequence operably linked thereto. For purposes of the present invention, a promoter sequence includes the minimum number of bases or elements necessary to initiate transcription of a gene of interest at levels detectable above background. Within the promoter sequence is a transcription initiation site, as well as  
15 protein binding domains (consensus sequences) responsible for the binding of RNA polymerase. Eucaryotic promoters will often, but not always, contain "TATA" boxes and "CAT" boxes.

A control sequence "directs the transcription" of a coding sequence in a cell when RNA polymerase will bind the promoter sequence and transcribe the coding  
20 sequence into mRNA, which is then translated into the polypeptide encoded by the coding sequence.

"Expression cassette" or "expression construct" refers to an assembly which is capable of directing the expression of the sequence(s) or gene(s) of interest. The expression cassette includes control elements, as described above, such as a promoter  
25 which is operably linked to (so as to direct transcription of) the sequence(s) or gene(s) of interest, and often includes a polyadenylation sequence as well. Within certain embodiments of the invention, the expression cassette described herein may be contained within a plasmid construct. In addition to the components of the expression cassette, the plasmid construct may also include, one or more selectable markers, a  
30 signal which allows the plasmid construct to exist as single-stranded DNA (e.g., a M13 origin of replication), at least one multiple cloning site, and a "mammalian" origin of replication (e.g., a SV40 or adenovirus origin of replication).

“Transformation,” as used herein, refers to the insertion of an exogenous polynucleotide into a host cell, irrespective of the method used for insertion: for example, transformation by direct uptake, transfection, infection, and the like. For particular methods of transfection, see further below. The exogenous polynucleotide  
5 may be maintained as a nonintegrated vector, for example, an episome, or alternatively, may be integrated into the host genome.

A “host cell” is a cell which has been transformed, or is capable of transformation, by an exogenous DNA sequence.

By “isolated” is meant, when referring to a polypeptide, that the indicated  
10 molecule is separate and discrete from the whole organism with which the molecule is found in nature or is present in the substantial absence of other biological macromolecules of the same type. The term “isolated” with respect to a polynucleotide is a nucleic acid molecule devoid, in whole or part, of sequences normally associated with it in nature; or a sequence, as it exists in nature, but having heterologous sequences in  
15 association therewith; or a molecule disassociated from the chromosome.

The term “purified” as used herein preferably means at least 75% by weight, more preferably at least 85% by weight, more preferably still at least 95% by weight, and most preferably at least 98% by weight, of biological macromolecules of the same type are present.

20 “Homology” refers to the percent identity between two polynucleotide or two polypeptide moieties. Two DNA, or two polypeptide sequences are “substantially homologous” to each other when the sequences exhibit at least about 50% , preferably at least about 75%, more preferably at least about 80%-85%, preferably at least about 90%, and most preferably at least about 95%-98%, or more, sequence identity over a  
25 defined length of the molecules. As used herein, substantially homologous also refers to sequences showing complete identity to the specified DNA or polypeptide sequence. The term “substantially homologous” as used herein in reference to  $\Delta$ NS35 generally refers to an HCV nucleic or amino acid sequence that is at least 60% identical to the entire sequence of the polypeptide encoded by  $\Delta$ NS35 (see FIG. 5), where the sequence  
30 identity is preferably at least 75%, more preferably at least 80%, still more preferably at least about 85%, especially more than about 90%, most preferably 95% or greater, particularly 98% or greater. These homologous polypeptides include fragments,

including mutants and allelic variants of the fragments. Identity between the two sequences is preferably determined by the Smith-Waterman homology search algorithm as implemented in the MPSRCH program (Oxford Molecular), using an affine gap search with parameters *gap open penalty*=12 and *gap extension penalty*=1. Thus, for  
5 example, the present invention includes an isolate which is 80% identical to a polypeptide encoded by  $\Delta$ NS35. In some aspects of the invention, the polypeptide of the present invention is substantially homologous to the  $\Delta$ NS35.

In general, "identity" refers to an exact nucleotide-to-nucleotide or amino acid-to-amino acid correspondence of two polynucleotides or polypeptide sequences,  
10 respectively. Percent identity can be determined by a direct comparison of the sequence information between two molecules by aligning the sequences, counting the exact number of matches between the two aligned sequences, dividing by the length of the shorter sequence, and multiplying the result by 100. Readily available computer programs can be used to aid in the analysis, such as ALIGN, Dayhoff, M.O. in *Atlas of*  
15 *Protein Sequence and Structure* M.O. Dayhoff ed., 5 Suppl. 3:353-358, National biomedical Research Foundation, Washington, DC, which adapts the local homology algorithm of Smith and Waterman *Advances in Appl. Math.* 2:482-489, 1981 for peptide analysis. Programs for determining nucleotide sequence identity are available in the Wisconsin Sequence Analysis Package, Version 8 (available from Genetics  
20 Computer Group, Madison, WI) for example, the BESTFIT, FASTA and GAP programs, which also rely on the Smith and Waterman algorithm. These programs are readily utilized with the default parameters recommended by the manufacturer and described in the Wisconsin Sequence Analysis Package referred to above. For example, percent identity of a particular nucleotide sequence to a reference sequence  
25 can be determined using the homology algorithm of Smith and Waterman with a default scoring table and a gap penalty of six nucleotide positions.

Another method of establishing percent identity in the context of the present invention is to use the MPSRCH package of programs copyrighted by the University of Edinburgh, developed by John F. Collins and Shane S. Sturrok, and distributed by  
30 IntelliGenetics, Inc. (Mountain View, CA). From this suite of packages the Smith-Waterman algorithm can be employed where default parameters are used for the scoring table (for example, gap open penalty of 12, gap extension penalty of one, and a

gap of six). From the data generated the "Match" value reflects "sequence identity." Other suitable programs for calculating the percent identity or similarity between sequences are generally known in the art, for example, another alignment program is BLAST, used with default parameters. For example, BLASTN and BLASTP can be  
5 used using the following default parameters: genetic code = standard; filter = none; strand = both; cutoff = 60; expect = 10; Matrix = BLOSUM62; Descriptions = 50 sequences; sort by = HIGH SCORE; Databases = non-redundant, GenBank + EMBL + DDBJ + PDB + GenBank CDS translations + Swiss protein + Spupdate + PIR. Details of these programs can be found at the following internet address:  
10 <http://www.ncbi.nlm.gov/cgi-bin/BLAST>.

Alternatively, homology can be determined by hybridization of polynucleotides under conditions which form stable duplexes between homologous regions, followed by digestion with single-stranded-specific nuclease(s), and size determination of the digested fragments. DNA sequences that are substantially homologous can be  
15 identified in a Southern hybridization experiment under, for example, stringent conditions, as defined for that particular system. Defining appropriate hybridization conditions is within the skill of the art. See, e.g., Sambrook et al., *supra*; *DNA Cloning, supra*; *Nucleic Acid Hybridization, supra*.

"Stringency" refers to conditions in a hybridization reaction that favor  
20 association of very similar sequences over sequences that differ. For example, the combination of temperature and salt concentration should be chosen that is approximately 120 to 200°C below the calculated  $T_m$  of the hybrid under study. The temperature and salt conditions can often be determined empirically in preliminary experiments in which samples of genomic DNA immobilized on filters are hybridized  
25 to the sequence of interest and then washed under conditions of different stringencies. See Sambrook *et al.* at page 9.50.

Variables to consider when performing, for example, a Southern blot are (1) the complexity of the DNA being blotted and (2) the homology between the probe and the sequences being detected. The total amount of the fragment(s) to be studied can vary a  
30 magnitude of 10, from 0.1 to 1 µg for a plasmid or phage digest to  $10^{-9}$  to  $10^{-8}$  g for a single copy gene in a highly complex eukaryotic genome. For lower complexity polynucleotides, substantially shorter blotting, hybridization, and exposure times, a



smaller amount of starting polynucleotides, and lower specific activity of probes can be used. For example, a single-copy yeast gene can be detected with an exposure time of only 1 hour starting with 1 µg of yeast DNA, blotting for two hours, and hybridizing for 4-8 hours with a probe of  $10^8$  cpm/µg. For a single-copy mammalian gene a conservative approach would start with 10 µg of DNA, blot overnight, and hybridize overnight in the presence of 10% dextran sulfate using a probe of greater than  $10^8$  cpm/µg, resulting in an exposure time of ~24 hours.

Several factors can affect the melting temperature ( $T_m$ ) of a DNA-DNA hybrid between the probe and the fragment of interest, and consequently, the appropriate conditions for hybridization and washing. In many cases the probe is not 100% homologous to the fragment. Other commonly encountered variables include the length and total G+C content of the hybridizing sequences and the ionic strength and formamide content of the hybridization buffer. The effects of all of these factors can be approximated by a single equation:

$$T_m = 81 + 16.6(\log_{10} C_i) + 0.4[\%(G + C)] - 0.6(\% \text{formamide}) - 600/n - 1.5(\% \text{mismatch}).$$
where  $C_i$  is the salt concentration (monovalent ions) and  $n$  is the length of the hybrid in base pairs (slightly modified from Meinkoth & Wahl (1984) *Anal. Biochem.* 138: 267-284). In general, convenient hybridization temperatures in the presence of 50% formamide are 42°C for a probe with is 95% to 100% homologous to the target fragment, 37°C for 90% to 95% homology, and 32°C for 85% to 90% homology. For lower homologies, formamide content should be lowered and temperature adjusted accordingly, using the equation above. If the homology between the probe and the target fragment are not known, the simplest approach is to start with both hybridization and wash conditions which are nonstringent. If non-specific bands or high background are observed after autoradiography, the filter can be washed at high stringency and reexposed. If the time required for exposure makes this approach impractical, several hybridization and/or washing stringencies should be tested in parallel.

By "nucleic acid immunization" is meant the introduction of a nucleic acid molecule encoding one or more selected antigens into a host cell, for the *in vivo* expression of the antigen or antigens. The nucleic acid molecule can be introduced directly into the recipient subject, such as by injection, inhalation, oral, intranasal and mucosal administration, or the like, or can be introduced *ex vivo*, into cells which have

been removed from the host. In the latter case, the transformed cells are reintroduced into the subject where an immune response can be mounted against the antigen encoded by the nucleic acid molecule.

5 An "open reading frame" or ORF is a region of a polynucleotide sequence which encodes a polypeptide; this region can represent a portion of a coding sequence or a total coding sequence.

As used herein, the term "antibody" refers to a polypeptide or group of polypeptides which comprise at least one antigen binding site. An "antigen binding site" is formed from the folding of the variable domains of an antibody molecule(s) to form three-dimensional binding sites with an internal surface shape and charge distribution complementary to the features of an epitope of an antigen, which allows specific binding to form an antibody-antigen complex. An antigen binding site may be formed from a heavy- and/or light-chain domain (VH and VL, respectively), which form hypervariable loops which contribute to antigen binding. The term "antibody" includes, without limitation, polyclonal antibodies, monoclonal antibodies, chimeric antibodies, altered antibodies, univalent antibodies, Fab proteins, and single-domain antibodies. In many cases, the binding phenomena of antibodies to antigens is equivalent to other ligand/anti-ligand binding.

15 If polyclonal antibodies are desired, a selected mammal (e.g., mouse, rabbit, goat, horse, etc.) is immunized with an immunogenic polypeptide bearing an HCV epitope(s). Serum from the immunized animal is collected and treated according to known procedures. If serum containing polyclonal antibodies to an HCV epitope contains antibodies to other antigens, the polyclonal antibodies can be purified by immunoaffinity chromatography. Techniques for producing and processing polyclonal antisera are known in the art, see for example, Mayer and Walker, eds. (1987) IMMUNOCHEMICAL METHODS IN CELL AND MOLECULAR BIOLOGY (Academic Press, London).

20 Monoclonal antibodies directed against HCV epitopes can also be readily produced by one skilled in the art. The general methodology for making monoclonal antibodies by hybridomas is well known. Immortal antibody-producing cell lines can be created by cell fusion, and also by other techniques such as direct transformation of B lymphocytes with oncogenic DNA, or transfection with Epstein-Barr virus. See, e.g.,

M. Schreier et al. (1980) HYBRIDOMA TECHNIQUES; Hammerling et al. (1981), MONOCLONAL ANTIBODIES AND T-CELL HYBRIDOMAS; Kennett et al. (1980) MONOCLONAL ANTIBODIES; see also, U.S. Pat. Nos. 4,341,761; 4,399,121; 4,427,783; 4,444,887; 4,466,917; 4,472,500; 4,491,632; and 4,493,890. Panels of  
5 monoclonal antibodies produced against HCV epitopes can be screened for various properties; i.e., for isotype, epitope affinity, etc. As used herein, a "single domain antibody" (dAb) is an antibody which is comprised of an HL domain, which binds specifically with a designated antigen. A dAb does not contain a VL domain, but may contain other antigen binding domains known to exist to antibodies, for example, the  
10 kappa and lambda domains. Methods for preparing dabs are known in the art. See, for example, Ward et al, Nature 341: 544 (1989).

Antibodies can also be comprised of VH and VL domains, as well as other known antigen binding domains. Examples of these types of antibodies and methods for their preparation and known in the art (see, e.g., U.S. Pat. No. 4,816,467), and  
15 include the following. For example, "vertebrate antibodies" refers to antibodies which are tetramers or aggregates thereof, comprising light and heavy chains which are usually aggregated in a "Y" configuration and which may or may not have covalent linkages between the chains. In vertebrate antibodies, the amino acid sequences of the chains are homologous with those sequences found in antibodies produced in  
20 vertebrates, whether in situ or in vitro (for example, in hybridomas). Vertebrate antibodies include, for example, purified polyclonal antibodies and monoclonal antibodies, methods for the preparation of which are described infra.

"Hybrid antibodies" are antibodies where chains are separately homologous with reference to mammalian antibody chains and represent novel assemblies of them,  
25 so that two different antigens are precipitable by the tetramer or aggregate. In hybrid antibodies, one pair of heavy and light chains are homologous to those found in an antibody raised against a first antigen, while a second pair of chains are homologous to those found in an antibody raised against a second antibody. This results in the property of "divalence", i.e., the ability to bind two antigens simultaneously. Such hybrids can  
30 also be formed using chimeric chains, as set forth below.

"Chimeric antibodies" refers to antibodies in which the heavy and/or light chains are fusion proteins. Typically, one portion of the amino acid sequences of the

chain is homologous to corresponding sequences in an antibody derived from a particular species or a particular class, while the remaining segment of the chain is homologous to the sequences derived from another species and/or class. Usually, the variable region of both light and heavy chains mimics the variable regions or antibodies  
5 derived from one species of vertebrates, while the constant portions are homologous to the sequences in the antibodies derived from another species of vertebrates. However, the definition is not limited to this particular example. Also included is any antibody in which either or both of the heavy or light chains are composed of combinations of sequences mimicking the sequences in antibodies of different sources, whether these  
10 sources be from differing classes or different species of origin, and whether or not the fusion point is at the variable/constant boundary. Thus, it is possible to produce antibodies in which neither the constant nor the variable region mimic known antibody sequences. It then becomes possible, for example, to construct antibodies whose variable region has a higher specific affinity for a particular antigen, or whose constant  
15 region can elicit enhanced complement fixation, or to make other improvements in properties possessed by a particular constant region.

Another example is "altered antibodies", which refers to antibodies in which the naturally occurring amino acid sequence in a vertebrate antibody has been varied. Utilizing recombinant DNA techniques, antibodies can be redesigned to obtain desired  
20 characteristics. The possible variations are many, and range from the changing of one or more amino acids to the complete redesign of a region, for example, the constant region. Changes in the constant region, in general, to attain desired cellular process characteristics, e.g., changes in complement fixation, interaction with membranes, and other effector functions. Changes in the variable region can be made to alter antigen  
25 binding characteristics. The antibody can also be engineered to aid the specific delivery of a molecule or substance to a specific cell or tissue site. The desired alterations can be made by known techniques in molecular biology, e.g., recombinant techniques, site-directed mutagenesis, etc.

Yet another example are "univalent antibodies", which are aggregates  
30 comprised of a heavy-chain/light-chain dimer bound to the Fc (i.e., stem) region of a second heavy chain. This type of antibody escapes antigenic modulation. See, e.g., Glennie et al. Nature 295: 712 (1982). Included also within the definition of antibodies

are "Fab" fragments of antibodies. The "Fab" region refers to those portions of the heavy and light chains which are roughly equivalent, or analogous, to the sequences which comprise the branch portion of the heavy and light chains, and which have been shown to exhibit immunological binding to a specified antigen, but which lack the effector Fc portion. "Fab" includes aggregates of one heavy and one light chain (commonly known as Fab'), as well as tetramers containing the 2H and 2L chains (referred to as F(ab)2), which are capable of selectively reacting with a designated antigen or antigen family. Fab antibodies can be divided into subsets analogous to those described above, i.e., "vertebrate Fab", "hybrid Fab", "chimeric Fab", and "altered Fab".

Methods of producing Fab fragments of antibodies are known within the art and include, for example, proteolysis, and synthesis by recombinant techniques.

"Antigen-antibody complex" refers to the complex formed by an antibody that is specifically bound to an epitope on an antigen.

"Immunogenic polypeptide" refers to a polypeptide that elicits a cellular and/or humoral immune response in a mammal, whether alone or linked to a carrier, in the presence or absence of an adjuvant.

"Antigenic determinant" refers to the site on an antigen or hapten to which a specific antibody molecule or specific cell surface receptor binds.

As used herein, "treatment" refers to any of (i) the prevention of infection or reinfection, as in a traditional vaccine, (ii) the reduction or elimination of symptoms, and (iii) the substantial or complete elimination of the pathogen in question. Treatment may be effected prophylactically (prior to infection) or therapeutically (following infection).

By "vertebrate subject" is meant any member of the subphylum cordata, including, without limitation, humans and other primates, including non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs; birds, including domestic, wild and game birds such as chickens, turkeys and other gallinaceous birds, ducks, geese, and the like. The term does not denote a particular age. Thus, both adult and newborn individuals are intended to be covered. The

invention described herein is intended for use in any of the above vertebrate species, since the immune systems of all of these vertebrates operate similarly.

## II. Modes of Carrying out the Invention

5        Before describing the present invention in detail, it is to be understood that this invention is not limited to particular formulations or process parameters as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

10        Although a number of compositions and methods similar or equivalent to those described herein can be used in the practice of the present invention, the preferred materials and methods are described herein.

### General Overview

15        An aim of an HCV vaccine is to generate broad immunity to a wide breadth of antigens because HCV is so divergent and because humoral as well as cellular immune responses are desirable to combat this human pathogen. While antibodies generated against the envelope glycoprotein(s) might aid in virus neutralization, there is additional benefit to be derived from a vaccine that includes other regions. The  
20        likelihood of T-helper responses generated against a polypeptide would be helpful in a vaccine setting as would generation of cytotoxic T cells. The non-structural region represents such a candidate antigen, but processing by the protease generates several polypeptides, making purification complicated. It would be advantageous, therefore, to derive a non-structural cassette that is unprocessed by the NS3 protease.

25        The present invention solves this and other problems using compositions and methods involving an N-terminal deletion in NS3, which removes the catalytic domain. As such, some or all of the remainder of the non-structural region (through NS5B) is expressed as an intact polypeptide. Expression of this species has been documented in mammalian cells as well as in yeast. Further, in certain aspects, polynucleotides  
30        encoding HCV core polypeptides (or fragments thereof) are added (*e.g.*, operably linked) to the carboxy-terminus of the non-structural cassette. As the core coding region is relatively highly conserved among HCV isolates, the presence of this region

may enhance the immune response. Because core has at its C-terminus a very hydrophobic domain (amino acids 174-191), shorter versions of core were also engineered onto the polypeptide. As described in detail herein, the truncation of core to amino acid 121 yielded higher expression than the amino acid 173 truncation when engineered onto the C-terminus of the mutant NS polypeptide. The combination of most of the non-structural region fused to a C-terminally truncated core into a polypeptide is novel and has advantages for vaccine immunization. Moreover, because the aim is not necessarily to generate antibody responses to this polypeptide, there is no need to maintain a native conformation, enabling a more facile purification protocol.

### **Mutant HCV Non-Structural Polypeptides**

Genomes of HCV strains contain a single open reading frame of approximately 9,000 to 12,000 nucleotides, which is transcribed into a polyprotein. An HCV polyprotein is cleaved to produce at least ten distinct products, in the order of NH<sub>2</sub>-Core-E1-E2-p7-NS2-NS3-NS4a-NS4b-NS5a-NS5b-COOH. Mutant HCV polypeptides of the invention contain an N-terminal deletion in NS3, which removes or disables the catalytic domain. Preferably, the polypeptides also include the remainder of the non-structural region, although in certain embodiments, the polypeptides may include less than all of the remaining NS polypeptides, for example mutant NS polypeptides including any combinations of NS2-NS3-NS4a-NS4b-NS5a-NS5b (e.g., NS3NS3-NS5a-NS5b; NS3-NS4a-NS4b; NS3-NS4a-NS4b-NS5a; NS3-NS4b-NS5a-NS5b; NS3-NS4a-NS5a; NS3-NS4b-NS5a; NS3-NS4b-NS5b; etc.).

The HCV NS3 protein functions as a protease and a helicase and occurs at approximately amino acid 1027 to amino acid 1657 of the polyprotein (numbered relative to HCV-1). See Choo *et al.* (1991) Proc. Natl. Acad. Sci. USA 88:2451-2455. HCV NS4 occurs at approximately amino acid 1658 to amino acid 1972, NS5a occurs at approximately amino acid 1973 to amino acid 2420, and HCV NS5b occurs at approximately amino acid 2421 to amino acid 3011 of the polyprotein (numbered relative to HCV-1) (Choo *et al.*, 1991).

The mutant polypeptides described herein can either be full-length polypeptides or portions of NS3, NS4 (NS4a and NS4b), NS5a, and NS5b polypeptides. Epitopes of NS3, NS4 (NS4a and NS4b), NS5a, NS5b, NS3NS4NS5a, and NS3NS4NS5aNS5b can

be identified by several methods. For example, NS3, NS4, NS5a, NS5b polypeptides or fusion proteins comprising any combination of the above, can be isolated, for example, by immunoaffinity purification using a monoclonal antibody for the polypeptide or protein. The isolated protein sequence can then be screened by  
5 preparing a series of short peptides by proteolytic cleavage of the purified protein, which together span the entire protein sequence. By starting with, for example, 100-mer polypeptides, each polypeptide can be tested for the presence of epitopes recognized by a T cell receptor on an HCV-activated T cell, progressively smaller and overlapping fragments can then be tested from an identified 100-mer to map the epitope  
10 of interest.

Epitopes recognized by a T cell receptor on an HCV-activated T cell can be identified by, for example,  $^{51}\text{Cr}$  release assay (see Example 2) or by lymphoproliferation assay (see Example 4). In a  $^{51}\text{Cr}$  release assay, target cells can be constructed that display the epitope of interest by cloning a polynucleotide encoding the  
15 epitope into an expression vector and transforming the expression vector into the target cells. Non-structural polypeptides can occur in any order in the fusion protein. If desired, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more of one or more of the polypeptides may occur in the fusion protein. Multiple viral strains of HCV occur, and NS3, NS4, NS5a, and NS5b polypeptides of any of these strains can be used in a fusion protein.

20 Nucleic acid and amino acid sequences of a number of HCV strains and isolates, including nucleic acid and amino acid sequences of NS3, NS4, NS5a, NS5b genes and polypeptides have been determined. For example, isolate HCV J1.1 is described in Kubo *et al.* (1989) Japan. Nucl. Acids Res. 17:10367-10372; Takeuchi *et al.* (1990) Gene 91:287-291; Takeuchi *et al.* (1990) J. Gen. Virol. 71:3027-3033; and  
25 Takeuchi *et al.* (1990) Nucl. Acids Res. 18:4626. The complete coding sequences of two independent isolates, HCV-J and BK, are described by Kato *et al.*, (1990) Proc. Natl. Acad. Sci. USA 87:9524-9528 and Takamizawa *et al.*, (1991) J. Virol. 65:1105-1113 respectively.

Publications that describe HCV-1 isolates include Choo *et al.* (1990) Brit. Med.  
30 Bull. 46:423-441; Choo *et al.* (1991) Proc. Natl. Acad. Sci. USA 88:2451-2455 and Han *et al.* (1991) Proc. Natl. Acad. Sci. USA 88:1711-1715. HCV isolates HC-J1 and HC-J4 are described in Okamoto *et al.* (1991) Japan J. Exp. Med. 60:167-177. HCV



isolates HCT 18~, HCT 23, Th, HCT 27, EC1 and EC10 are described in Weiner *et al.* (1991) *Virol.* 180:842-848. HCV isolates Pt-1, HCV-K1 and HCV-K2 are described in Enomoto *et al.* (1990) *Biochem. Biophys. Res. Commun.* 170:1021-1025. HCV isolates A, C, D & E are described in Tsukiyama-Kohara *et al.* (1991) *Virus Genes* 5:243-254.

Each of the mutant HCV polypeptides containing at least portions of NS3, NS4 and NS5 can be obtained from the same HCV strain or isolate or from different HCV strains or isolates. Thus, each non-structural region of the polypeptide can be from the same HCV strain or isolate or from each different HCV strains or isolates. In addition to the mutant HCV non-structural polypeptides described herein, the proteins can contain other polypeptides derived from the HCV polyprotein. For example, it may be desirable to include polypeptides derived from the core region of the HCV polyprotein. This region occurs at amino acid positions 1-191 of the HCV polyprotein, numbered relative to HCV-1. Either the full-length protein or epitopes of the full-length protein may be used in the subject fusions, such as those epitopes found between amino acids 10-53, amino acids 10-45, amino acids 67-88, amino acids 120-130, or any of the core epitopes identified in, e.g., Houghton *et al.*, U.S. Patent No. 5,350,671; Chien *et al.*, *Proc. Natl. Acad. Sci. USA* (1992) 89:10011-10015; Chien *et al.*, *J. Gastroent. Hepatol.* (1993) 8:S33-39; Chien *et al.*, International Publication No. WO 93/00365; Chien, D.Y., International Publication No. WO 94/01778; and commonly owned, U.S. Patent No. 6,150,087. When present, additional non-structural HCV polypeptides such as core can be obtained from the same HCV strain or isolate or from different HCV strains or isolates.

Preferably, the above-described mutant proteins, as well as the individual components of these proteins, are produced recombinantly. A polynucleotide encoding these proteins can be introduced into an expression vector which can be expressed in a suitable expression system. A variety of bacterial, yeast, mammalian, insect and plant expression systems are available in the art and any such expression system can be used. Optionally, a polynucleotide encoding these proteins can be translated in a cell-free translation system. Such methods are well known in the art. The proteins also can be constructed by solid phase protein synthesis.

If desired, the mutant polypeptides, or the individual components of these polypeptides, also can contain other amino acid sequences, such as amino acid linkers or signal sequences, as well as ligands useful in protein purification, such as glutathione-S-transferase and staphylococcal protein A.

5

### **Polynucleotides**

The polynucleotides of the present invention are not necessarily physically derived from the nucleotide sequences shown, but can be generated in any manner, including, for example, chemical synthesis or DNA replication or reverse transcription or transcription. In addition, combinations of regions corresponding to that of the designated sequences can be modified in ways known to the art to be consistent with an intended use.

The DNA encoding the desired polypeptide, whether in fused or mature form, and whether or not containing a signal sequence to permit secretion, can be ligated into expression vectors suitable for any convenient host. Both eukaryotic and prokaryotic host systems are presently used in forming recombinant polypeptides, and a summary of some of the more common control systems and host cell is given below. The polypeptide produced in such host cells is then isolated from lysed cells or from the culture medium and purified to the extent needed for its intended use.

Purification can be by techniques known in the art, for example, differential extraction, salt fractionation, chromatography on ion exchange resins, affinity chromatography, centrifugation, alkali resolubilization of insoluble protein, and the like. See, for example, Methods in Enzymology for a variety of methods for purifying proteins.

Polynucleotides contain less than an entire HCV genome and can be RNA or single- or double-stranded DNA. Preferably, the polynucleotides are isolated free of other components, such as proteins and lipids. Polynucleotides of the invention can also comprise other nucleotide sequences, such as sequences coding for linkers, signal sequences, or ligands useful in protein purification such as glutathione-S-transferase and staphylococcal protein A.

Polynucleotides encoding mutant HCV non-structural polypeptides can be isolated from a genomic library derived from nucleic acid sequences present in, for

example, the plasma, serum, or liver homogenate of an HCV infected individual or can be synthesized in the laboratory, for example, using an automatic synthesizer. An amplification method such as PCR can be used to amplify polynucleotides from either HCV genomic DNA or cDNA.

5 Further, while the polypeptides that are not NS3, NS4, or NS5 of HCV of the present invention can comprise a substantially complete viral domain, in many applications all that is required is that the polypeptide comprise an antigenic or immunogenic region of the virus. An antigenic region of a polypeptide is generally relatively small-typically 8 to 10 amino acids or less in length. Fragments of as few as 5  
10 amino acids can characterize an antigenic region. These segments can correspond to regions of, for example, C, E1, or E2 epitopes. Accordingly, using the cDNAs of C, E1, or E2 as a basis, DNAs encoding short segments of C, E1, or E2 polypeptides can be expressed recombinantly either as fusion proteins, or as isolated polypeptides. In addition, short amino acid sequences can be conveniently obtained by chemical  
15 synthesis.

Polynucleotides encoding the polypeptides described herein can comprise coding sequences for these polypeptides which occur naturally or can be artificial sequences which do not occur in nature. These polynucleotides can be ligated to form a coding sequence for the fusion proteins using standard molecular biology techniques.  
20 If desired, polynucleotides can be cloned into an expression vector and transformed into, for example, bacterial, yeast, insect, plant or mammalian cells so that the fusion proteins of the invention can be expressed in and isolated from a cell culture.

The expression of polypeptides containing these domains in a variety of recombinant host cells, including, for example, bacteria, yeast, insect, plant and  
25 vertebrate cells, give rise to important immunological reagents which can be used for diagnosis, detection, and vaccines.

The general techniques used in extracting the genome from a virus, preparing and probing a cDNA library, sequencing clones, constructing expression vectors, transforming cells, performing immunological assays such as radioimmunoassays and  
30 ELISA assays, for growing cells in culture, and the like are known in the art and laboratory manuals are available describing these techniques. However, as a general

guide, the following sets forth some sources currently available for such procedures, and for materials useful in carrying them out.

Both prokaryotic and eukaryotic host cells may be used for expression of desired coding sequences when appropriate control sequences which are compatible  
5 with the designated host are used. Among prokaryotic hosts, *E. coli* is most frequently used. Expression control sequences for prokaryotes include promoters, optionally containing operator portions, and ribosome binding sites. Transfer vectors compatible with prokaryotic hosts are commonly derived from, for example, pBR322, a plasmid containing operons conferring ampicillin and tetracycline resistance, and the various  
10 pUC vectors, which also contain sequences conferring antibiotic resistance markers. These markers may be used to obtain successful transformants by selection. Commonly used prokaryotic control sequences include the Beta-lactamase (penicillinase) and lactose promoter systems (Chang et al. (1977), *Nature* 198:1056), the tryptophan (*trp*) promoter system (Goeddel et al. (1980) *Nucleic Acid Res.* 8:4057), the lambda-derived  
15 P[L ]promoter and N gene ribosome binding site (Shimatake et al. (1981) *Nature* 292:128) and the hybrid *tac* promoter (De Boer et al. (1983) *Proc. Natl. Acad. Sci. U.S.A.* 292:128) derived from sequences of the *trp* and *lac UV5* promoters. The foregoing systems are particularly compatible with *E. coli*; if desired, other prokaryotic hosts such as strains of *Bacillus* or *Pseudomonas* may be used, with corresponding  
20 control sequences.

Eukaryotic hosts include mammalian and yeast cells in culture systems. Mammalian cell lines available as hosts for expression are known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), including HeLa cells, Chinese hamster ovary (CHO) cells, baby hamster  
25 kidney (BHK) cells, and a number of other cell lines. Suitable promoters for mammalian cells are also known in the art and include viral promoters such as that from Simian Virus 40 (SV40) (Fiers (1978), *Nature* 273:113), Rous sarcoma virus (RSV), adenovirus (ADV), and bovine papilloma virus (BPV). Mammalian cells may also require terminator sequences and poly A addition sequences; enhancer sequences  
30 which increase expression may also be included, and sequences which cause amplification of the gene may also be desirable. These sequences are known in the art. Vectors suitable for replication in mammalian cells may include viral replicons, or

sequences which insure integration of the appropriate sequences encoding NANBV epitopes into the host genome.

The vaccinia virus system can also be used to express foreign DNA in mammalian cells. To express heterologous genes, the foreign DNA is usually inserted  
5 into the thymidine kinase gene of the vaccinia virus and then infected cells can be selected. This procedure is known in the art and further information can be found in these references (Mackett et al. J. Virol. 49: 857-864 (1984) and Chapter 7 in DNA Cloning, Vol. 2, IRL Press).

Yeast expression systems are also known to one of ordinary skill in the art. A  
10 yeast promoter is any DNA sequence capable of binding yeast RNA polymerase and initiating the downstream (3') transcription of a coding sequence (e.g., structural gene) into mRNA. A promoter will have a transcription initiation region which is usually placed proximal to the 5' end of the coding sequence. This transcription initiation region usually includes an RNA polymerase binding site (the "TATA Box") and a  
15 transcription initiation site. A yeast promoter may also have a second domain called an upstream activator sequence (UAS), which, if present, is usually distal to the structural gene. The UAS permits regulated (inducible) expression. Constitutive expression occurs in the absence of a UAS. Regulated expression may be either positive or negative, thereby either enhancing or reducing transcription.

20 Yeast is a fermenting organism with an active metabolic pathway, therefore sequences encoding enzymes in the metabolic pathway provide particularly useful promoter sequences. Examples include alcohol dehydrogenase (ADH) (EP-A-0 284 044), enolase, glucokinase, glucose-6-phosphate isomerase, glyceraldehyde-3-phosphate-dehydrogenase (GAP or GAPDH), hexokinase, phosphofructokinase, 3-phosphoglycerate mutase, and pyruvate kinase (PyK) (EPO-A-0 329 203). The yeast  
25 *PHO5* gene, encoding acid phosphatase, also provides useful promoter sequences (Myanohara et al. (1983) *Proc. Natl. Acad. Sci. USA* 80:1).

In addition, synthetic promoters which do not occur in nature also function as yeast promoters. For example, UAS sequences of one yeast promoter may be joined  
30 with the transcription activation region of another yeast promoter, creating a synthetic hybrid promoter. Examples of such hybrid promoters include the ADH regulatory sequence linked to the GAP transcription activation region (US Patent Nos. 4,876,197

and 4,880,734). Other examples of hybrid promoters include promoters which consist of the regulatory sequences of either the *ADH2*, *GAL4*, *GAL10*, OR *PHO5* genes, combined with the transcriptional activation region of a glycolytic enzyme gene such as GAP or PyK (EP-A-0 164 556). Furthermore, a yeast promoter can include naturally occurring promoters of non-yeast origin that have the ability to bind yeast RNA polymerase and initiate transcription. Examples of such promoters include, *inter alia*, (Cohen *et al.* (1980) *Proc. Natl. Acad. Sci. USA* 77:1078; Henikoff *et al.* (1981) *Nature* 283:835; Hollenberg *et al.* (1981) *Curr. Topics Microbiol. Immunol.* 96:119; Hollenberg *et al.* (1979) "The Expression of Bacterial Antibiotic Resistance Genes in the Yeast *Saccharomyces cerevisiae*," in: *Plasmids of Medical, Environmental and Commercial Importance* (eds. K.N. Timmis and A. Puhler); Mercerau-Puigalon *et al.* (1980) *Gene* 11:163; Panthier *et al.* (1980) *Curr. Genet.* 2:109).

A DNA molecule may be expressed intracellularly in yeast. A promoter sequence may be directly linked with the DNA molecule, in which case the first amino acid at the N-terminus of the recombinant protein will always be a methionine, which is encoded by the ATG start codon. If desired, methionine at the N-terminus may be cleaved from the protein by *in vitro* incubation with cyanogen bromide.

Fusion proteins provide an alternative for yeast expression systems, as well as in mammalian, baculovirus, and bacterial expression systems. Usually, a DNA sequence encoding the N-terminal portion of an endogenous yeast protein, or other stable protein, is fused to the 5' end of heterologous coding sequences. Upon expression, this construct will provide a fusion of the two amino acid sequences. For example, the yeast or human superoxide dismutase (SOD) gene, can be linked at the 5' terminus of a foreign gene and expressed in yeast. The DNA sequence at the junction of the two amino acid sequences may or may not encode a cleavable site. See *e.g.*, EP-A-0 196 056. Another example is a ubiquitin fusion protein. Such a fusion protein is made with the ubiquitin region that preferably retains a site for a processing enzyme (*e.g.*, ubiquitin-specific processing protease) to cleave the ubiquitin from the foreign protein. Through this method, therefore, native foreign protein can be isolated (*e.g.*, WO88/024066).

Alternatively, foreign proteins can also be secreted from the cell into the growth media by creating chimeric DNA molecules that encode a fusion protein comprised of a

leader sequence fragment that provide for secretion in yeast of the foreign protein. Preferably, there are processing sites encoded between the leader fragment and the foreign gene that can be cleaved either *in vivo* or *in vitro*. The leader sequence fragment usually encodes a signal peptide comprised of hydrophobic amino acids  
5 which direct the secretion of the protein from the cell.

DNA encoding suitable signal sequences can be derived from genes for secreted yeast proteins, such as the yeast invertase gene (EP-A-0 012 873; JPO. 62,096,086) and the A-factor gene (US patent 4,588,684). Alternatively, leaders of non-yeast origin, such as an interferon leader, exist that also provide for secretion in yeast (EP-A-  
10 0 060 057).

A preferred class of secretion leaders are those that employ a fragment of the yeast alpha-factor gene, which contains both a "pre" signal sequence, and a "pro" region. The types of alpha-factor fragments that can be employed include the full-length pre-pro alpha factor leader (about 83 amino acid residues) as well as truncated  
15 alpha-factor leaders (usually about 25 to about 50 amino acid residues) (US Patents 4,546,083 and 4,870,008; EP-A-0 324 274). Additional leaders employing an alpha-factor leader fragment that provides for secretion include hybrid alpha-factor leaders made with a presequence of a first yeast, but a pro-region from a second yeast alphafactor. (e.g., see WO 89/02463.)

20 Usually, transcription termination sequences recognized by yeast are regulatory regions located 3' to the translation stop codon, and thus together with the promoter flank the coding sequence. These sequences direct the transcription of an mRNA which can be translated into the polypeptide encoded by the DNA. Examples of transcription terminator sequence and other yeast-recognized termination sequences,  
25 such as those coding for glycolytic enzymes.

Usually, the above described components, comprising a promoter, leader (if desired), coding sequence of interest, and transcription termination sequence, are put together into expression constructs. Expression constructs are often maintained in a replicon, such as an extrachromosomal element (e.g., plasmids) capable of stable  
30 maintenance in a host, such as yeast or bacteria. The replicon may have two replication systems, thus allowing it to be maintained, for example, in yeast for expression and in a prokaryotic host for cloning and amplification. Examples of such yeast-bacteria shuttle

vectors include YEp24 (Botstein *et al.* (1979) *Gene* 8:17-24), pCI/1 (Brake *et al.* (1984) *Proc. Natl. Acad. Sci USA* 81:4642-4646), and YRp17 (Stinchcomb *et al.* (1982) *J. Mol. Biol.* 158:157). In addition, a replicon may be either a high or low copy number plasmid. A high copy number plasmid will generally have a copy number ranging from about 5 to about 200, and usually about 10 to about 150. A host containing a high copy number plasmid will preferably have at least about 10, and more preferably at least about 20. Enter a high or low copy number vector may be selected, depending upon the effect of the vector and the foreign protein on the host. See *e.g.*, Brake *et al.*, *supra*.

Alternatively, the expression constructs can be integrated into the yeast genome with an integrating vector. Integrating vectors usually contain at least one sequence homologous to a yeast chromosome that allows the vector to integrate, and preferably contain two homologous sequences flanking the expression construct. Integrations appear to result from recombinations between homologous DNA in the vector and the yeast chromosome (Orr-Weaver *et al.* (1983) *Methods in Enzymol.* 101:228-245). An integrating vector may be directed to a specific locus in yeast by selecting the appropriate homologous sequence for inclusion in the vector. See Orr-Weaver *et al.*, *supra*. One or more expression construct may integrate, possibly affecting levels of recombinant protein produced (Rine *et al.* (1983) *Proc. Natl. Acad. Sci. USA* 80:6750). The chromosomal sequences included in the vector can occur either as a single segment in the vector, which results in the integration of the entire vector, or two segments homologous to adjacent segments in the chromosome and flanking the expression construct in the vector, which can result in the stable integration of only the expression construct.

Usually, extrachromosomal and integrating expression constructs may contain selectable markers to allow for the selection of yeast strains that have been transformed. Selectable markers may include biosynthetic genes that can be expressed in the yeast host, such as *ADE2*, *HIS4*, *LEU2*, *TRP1*, and *ALG7*, and the G418 resistance gene, which confer resistance in yeast cells to tunicamycin and G418, respectively. In addition, a suitable selectable marker may also provide yeast with the ability to grow in the presence of toxic compounds, such as metal. For example, the presence of *CUP1*



allows yeast to grow in the presence of copper ions (Butt *et al.* (1987) *Microbiol. Rev.* 51:351).

Alternatively, some of the above described components can be put together into transformation vectors. Transformation vectors are usually comprised of a selectable  
5 marker that is either maintained in a replicon or developed into an integrating vector, as described above.

Expression and transformation vectors, either extrachromosomal replicons or integrating vectors, have been developed for transformation into many yeasts. For example, expression vectors have been developed for, *inter alia*, the following yeasts:  
10 *Candida albicans* (Kurtz, *et al.* (1986) *Mol. Cell. Biol.* 6:142), *Candida maltosa* (Kunze, *et al.* (1985) *J. Basic Microbiol.* 25:141), *Hansenula polymorpha* (Gleeson, *et al.* (1986) *J. Gen. Microbiol.* 132:3459; Roggenkamp *et al.* (1986) *Mol. Gen. Genet.* 202:302), *Kluyveromyces fragilis* (Das, *et al.* (1984) *J. Bacteriol.* 158:1165), *Kluyveromyces lactis* (De Louvencourt *et al.* (1983) *J. Bacteriol.* 154:737; Van den  
15 Berg *et al.* (1990) *Bio/Technology* 8:135), *Pichia guilliermondii* (Kunze *et al.* (1985) *J. Basic Microbiol.* 25:141), *Pichia pastoris* (Cregg, *et al.* (1985) *Mol. Cell. Biol.* 5:3376; US Patent Nos. 4,837,148 and 4,929,555), *Saccharomyces cerevisiae* (Hinnen *et al.* (1978) *Proc. Natl. Acad. Sci. USA* 75:1929; Ito *et al.* (1983) *J. Bacteriol.* 153:163), *Schizosaccharomyces pombe* (Beach and Nurse (1981) *Nature* 300:706), and  
20 *Yarrowia lipolytica* (Davidow, *et al.* (1985) *Curr. Genet.* 10:380471 Gaillardin, *et al.* (1985) *Curr. Genet.* 10:49).

Methods of introducing exogenous DNA into yeast hosts are well-known in the art, and usually include either the transformation of spheroplasts or of intact yeast cells treated with alkali cations. Transformation procedures usually vary with the yeast  
25 species to be transformed. (See *e.g.*, Kurtz *et al.* (1986) *Mol. Cell. Biol.* 6:142; Kunze *et al.* (1985) *J. Basic Microbiol.* 25:141; *Candida*; Gleeson *et al.* (1986) *J. Gen. Microbiol.* 132:3459; Roggenkamp *et al.* (1986) *Mol. Gen. Genet.* 202:302; *Hansenula*; Das *et al.* (1984) *J. Bacteriol.* 158:1165; De Louvencourt *et al.* (1983) *J. Bacteriol.* 154:1165; Van den Berg *et al.* (1990) *Bio/Technology* 8:135;  
30 *Kluyveromyces*; Cregg *et al.* (1985) *Mol. Cell. Biol.* 5:3376; Kunze *et al.* (1985) *J. Basic Microbiol.* 25:141; US Patent Nos. 4,837,148 and 4,929,555; *Pichia*; Hinnen *et al.* (1978) *Proc. Natl. Acad. Sci. USA* 75:1929; Ito *et al.* (1983) *J. Bacteriol.*

153:163 *Saccharomyces*; Beach and Nurse (1981) *Nature* 300:706;  
*Schizosaccharomyces*; Davidow *et al.* (1985) *Curr. Genet.* 10:39; Gaillardin *et al.*  
(1985) *Curr. Genet.* 10:49; Yarrowia).

Bacterial expression techniques are known in the art. A bacterial promoter is  
5 any DNA sequence capable of binding bacterial RNA polymerase and initiating the  
downstream (3') transcription of a coding sequence (*e.g.*, structural gene) into mRNA.  
A promoter will have a transcription initiation region which is usually placed proximal  
to the 5' end of the coding sequence. This transcription initiation region usually  
includes an RNA polymerase binding site and a transcription initiation site. A bacterial  
10 promoter may also have a second domain called an operator, that may overlap an  
adjacent RNA polymerase binding site at which RNA synthesis begins. The operator  
permits negative regulated (inducible) transcription, as a gene repressor protein may  
bind the operator and thereby inhibit transcription of a specific gene. Constitutive  
expression may occur in the absence of negative regulatory elements, such as the  
15 operator. In addition, positive regulation may be achieved by a gene activator protein  
binding sequence, which, if present is usually proximal (5') to the RNA polymerase  
binding sequence. An example of a gene activator protein is the catabolite activator  
protein (CAP), which helps initiate transcription of the lac operon in *Escherichia coli*  
(*E. coli*) (Raibaud *et al.* (1984) *Annu. Rev. Genet.* 18:173). Regulated expression  
20 may therefore be either positive or negative, thereby either enhancing or reducing  
transcription.

Expression and transformation vectors, either extra-chromosomal replicons or  
integrating vectors, have been developed for transformation into many bacteria. For  
example, expression vectors have been developed for, *inter alia*, the following bacteria:  
25 *Bacillus subtilis* (Palva *et al.* (1982) *Proc. Natl. Acad. Sci. USA* 79:5582; EP-A-0  
036 259 and EP-A-0 063 953; WO 84/04541), *Escherichia coli* (Shimatake *et al.*  
(1981) *Nature* 292:128; Amann *et al.* (1985) *Gene* 40:183; Studier *et al.* (1986) *J.*  
*Mol. Biol.* 189:113; EP-A-0 036 776, EP-A-0 136 829 and EP-A-0 136 907),  
*Streptococcus cremoris* (Powell *et al.* (1988) *Appl. Environ. Microbiol.* 54:655);  
30 *Streptococcus lividans* (Powell *et al.* (1988) *Appl. Environ. Microbiol.* 54:655),  
*Streptomyces lividans* (US patent 4,745,056).

Methods of introducing exogenous DNA into bacterial hosts are well-known in the art, and usually include either the transformation of bacteria treated with  $\text{CaCl}_2$  or other agents, such as divalent cations and DMSO. DNA can also be introduced into bacterial cells by electroporation. Transformation procedures usually vary with the bacterial species to be transformed. (See *e.g.*, Masson *et al.* (1989) *FEMS Microbiol. Lett.* 60:273; Palva *et al.* (1982) *Proc. Natl. Acad. Sci. USA* 79:5582; EP-A-0 036 259 and EP-A-0 063 953; WO 84/04541, Bacillus, Miller *et al.* (1988) *Proc. Natl. Acad. Sci.* 85:856; Wang *et al.* (1990) *J. Bacteriol.* 172:949; Campylobacter, Cohen *et al.* (1973) *Proc. Natl. Acad. Sci.* 69:2110; Dower *et al.* (1988) *Nucleic Acids Res.* 16:6127; Kushner (1978) "An improved method for transformation of *Escherichia coli* with ColE1-derived plasmids. In *Genetic Engineering: Proceedings of the International Symposium on Genetic Engineering* (eds. H.W. Boyer and S. Nicosia); Mandel *et al.* (1970) *J. Mol. Biol.* 53:159; Taketo (1988) *Biochim. Biophys. Acta* 949:318; *Escherichia*; Chassy *et al.* (1987) *FEMS Microbiol. Lett.* 44:173 Lactobacillus; Fiedler *et al.* (1988) *Anal. Biochem* 170:38, *Pseudomonas*; Augustin *et al.* (1990) *FEMS Microbiol. Lett.* 66:203, *Staphylococcus*, Barany *et al.* (1980) *J. Bacteriol.* 144:698; Harlander (1987) "Transformation of *Streptococcus lactis* by electroporation, in: *Streptococcal Genetics* (ed. J. Ferretti and R. Curtiss III); Perry *et al.* (1981) *Infect. Immun.* 32:1295; Powell *et al.* (1988) *Appl. Environ. Microbiol.* 54:655; Somkuti *et al.* (1987) *Proc. 4th Eur. Cong. Biotechnology* 1:412, *Streptococcus*).

In addition, viral antigens can be expressed in insect cells by the Baculovirus system. A general guide to Baculovirus expression by Summer and Smith is *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures* (Texas Agricultural Experiment Station Bulletin No. 1555). To incorporate the heterologous gene into the Baculovirus genome the gene is first cloned into a transfer vector containing some Baculovirus sequences. This transfer vector, when it is cotransfected with wild-type virus into insect cells, will recombine with the wild-type virus. Usually, the transfer vector will be engineered so that the heterologous gene will disrupt the wild-type Baculovirus polyhedron gene. This disruption enables easy selection of the recombinant virus since the cells infected with the recombinant virus will appear phenotypically different from the cells infected with the wild-type virus. The purified

recombinant virus can be used to infect cells to express the heterologous gene. The foreign protein can be secreted into the medium if a signal peptide is linked in frame to the heterologous gene; otherwise, the protein will be bound in the cell lysates. For further information, see Smith et al *Mol. & Cell. Biol.* 3:2156-2165 (1983) or Luckow and Summers in *Virology* 17: 31-39 (1989).

Baculovirus expression can also be affected in plant cells. There are many plant cell culture and whole plant genetic expression systems known in the art. Exemplary plant cellular genetic expression systems include those described in patents, such as: US 5,693,506; US 5,659,122; and US 5,608,143. Additional examples of genetic expression in plant cell culture has been described by Zenk, *Phytochemistry* 30:3861-3863 (1991). Descriptions of plant protein signal peptides may be found in addition to the references described above in Vaulcombe et al., *Mol. Gen. Genet.* 209:33-40 (1987); Chandler et al., *Plant Molecular Biology* 3:407-418 (1984); Rogers, *J. Biol. Chem.* 260:3731-3738 (1985); Rothstein et al., *Gene* 55:353-356 (1987); Whittier et al., *Nucleic Acids Research* 15:2515-2535 (1987); Wirsal et al., *Molecular Microbiology* 3:3-14 (1989); Yu et al., *Gene* 122:247-253 (1992). A description of the regulation of plant gene expression by the phytohormone, gibberellic acid and secreted enzymes induced by gibberellic acid can be found in R.L. Jones and J. MacMillan, *Gibberellins*: in: *Advanced Plant Physiology*, Malcolm B. Wilkins, ed., 1984 Pitman Publishing Limited, London, pp. 21-52. References that describe other metabolically-regulated genes: Sheen, *Plant Cell*, 2:1027-1038(1990); Maas et al., *EMBO J.* 9:3447-3452 (1990); Benkel and Hickey, *Proc. Natl. Acad. Sci.* 84:1337-1339 (1987).

All plants from which protoplasts can be isolated and cultured to give whole regenerated plants can be transformed by the present invention so that whole plants are recovered which contain the transferred gene. It is known that practically all plants can be regenerated from cultured cells or tissues, including but not limited to all major species of sugarcane, sugar beet, cotton, fruit and other trees, legumes and vegetables. Some suitable plants include, for example, species from the genera *Fragaria*, *Lotus*, *Medicago*, *Onobrychis*, *Trifolium*, *Trigonella*, *Vigna*, *Citrus*, *Linum*, *Geranium*, *Manihot*, *Daucus*, *Arabidopsis*, *Brassica*, *Raphanus*, *Sinapis*, *Atropa*, *Capsicum*, *Datura*, *Hyoscyamus*, *Lycopersion*, *Nicotiana*, *Solanum*, *Petunia*, *Digitalis*, *Majorana*, *Cichorium*, *Helianthus*, *Lactuca*, *Bromus*, *Asparagus*, *Antirrhinum*, *Hererocallis*,

*Nemesia, Pelargonium, Panicum, Pennisetum, Ranunculus, Senecio, Salpiglossis, Cucumis, Browaalia, Glycine, Lolium, Zea, Triticum, Sorghum, and Datura.*

Transformation can be by any method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus and  
5 transducing a host cell with the virus, and by direct uptake of the polynucleotide. The transformation procedure used depends upon the host to be transformed. Bacterial transformation by direct uptake generally employs treatment with calcium or rubidium chloride (Cohen (1972), Proc. Natl. Acad. Sci. U.S.A. 69:2110; Maniatis et al. (1982), MOLECULAR CLONING; A LABORATORY MANUAL (Cold Spring Harbor Press,  
10 Cold Spring Harbor, N.Y.). Yeast transformation by direct uptake may be carried out using the method of Hinnen et al. (1978) Proc. Natl. Acad. Sci. U.S.A. 75: 1929. Mammalian transformations by direct uptake may be conducted using the calcium phosphate precipitation method of Graham and Van der Eb (1978), Virology 52:546 or the various known modifications thereof.

15 Vector construction employs techniques which are known in the art. Site-specific DNA cleavage is performed by treating with suitable restriction enzymes under conditions which generally are specified by the manufacturer of these commercially available enzymes. The cleaved fragments may be separated using polyacrylamide or agarose gel electrophoresis techniques, according to the general procedures found in  
20 Methods in Enzymology (1980) 65:499-560. Sticky ended cleavage fragments may be blunt ended using E. coli DNA polymerase I (Klenow) in the presence of the appropriate deoxynucleotide triphosphates (dNTPs) present in the mixture. Treatment with S1 nuclease may also be used, resulting in the hydrolysis of any single stranded DNA portions.

25 Ligations are carried out using standard buffer and temperature conditions using T4 DNA ligase and ATP; sticky end ligations require less ATP and less ligase than blunt end ligations. When vector fragments are used as part of a ligation mixture, the vector fragment is often treated with bacterial alkaline phosphatase (BAP) or calf intestinal alkaline phosphatase to remove the 5'-phosphate and thus prevent religation  
30 of the vector; alternatively, restriction enzyme digestion of unwanted fragments can be used to prevent ligation. Ligation mixtures are transformed into suitable cloning hosts,

such as *E. coli*, and successful transformants selected by, for example, antibiotic resistance, and screened for the correct construction.

Synthetic oligonucleotides may be prepared using an automated oligonucleotide synthesizer as described by Warner (1984), DNA 3:401. If desired, the synthetic strands  
5 may be labeled with  $^{32}\text{P}$  by treatment with polynucleotide kinase in the presence of  $^{32}\text{P}$ -ATP, using standard conditions for the reaction. DNA sequences, including those isolated from cDNA libraries, may be modified by known techniques, including, for example site directed mutagenesis, as described by Zoller (1982), Nucleic Acids Res. 10:6487.

10 The expression constructs of the present invention, including the desired fusion, or individual expression constructs comprising the individual components of these fusions, may be used for nucleic acid immunization, to activate HCV-specific T cells, using standard gene delivery protocols. Methods for gene delivery are known in the art. See, e.g., U.S. Patent Nos. 5,399,346, 5,580,859, 5,589,466. Genes can be  
15 delivered either directly to the vertebrate subject or, alternatively, delivered *ex vivo*, to cells derived from the subject and the cells reimplanted in the subject. For example, the constructs can be delivered as plasmid DNA, e.g., contained within a plasmid, such as pBR322, pUC, or ColE1

Additionally, the expression constructs can be packaged in liposomes prior to  
20 delivery to the cells. Lipid encapsulation is generally accomplished using liposomes which are able to stably bind or entrap and retain nucleic acid. The ratio of condensed DNA to lipid preparation can vary but will generally be around 1:1 (mg DNA:micromoles lipid), or more of lipid. For a review of the use of liposomes as carriers for delivery of nucleic acids, see, Hug and Sleight, *Biochim. Biophys. Acta*.  
25 (1991) 1097:1-17; Straubinger et al., in *Methods of Enzymology* (1983), Vol. 101, pp. 512-527.

Liposomal preparations for use with the present invention include cationic (positively charged), anionic (negatively charged) and neutral preparations, with cationic liposomes particularly preferred. Cationic liposomes are readily available. For  
30 example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, NY. (See, also, Felgner et al., *Proc. Natl. Acad. Sci. USA* (1987) 84:7413-7416). Other

commercially available lipids include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer). Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g., Szoka et al., *Proc. Natl. Acad. Sci. USA* (1978) 75:4194-4198; PCT Publication No. WO 90/11092 for a  
5 description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. The various liposome-nucleic acid complexes are prepared using methods known in the art. See, e.g., Straubinger et al., in *METHODS OF IMMUNOLOGY* (1983), Vol. 101, pp. 512-527; Szoka et al., *Proc. Natl. Acad. Sci. USA* (1978) 75:4194-4198; Papahadjopoulos et al., *Biochim. Biophys. Acta* (1975) 394:483; Wilson et al., *Cell* (1979) 17:77; Deamer and Bangham, *Biochim. Biophys. Acta* (1976) 443:629; Ostro et al., *Biochem. Biophys. Res. Commun.* (1977) 76:836; Fraley et al., *Proc. Natl. Acad. Sci. USA* (1979) 76:3348; Enoch and Strittmatter, *Proc. Natl. Acad. Sci. USA* (1979) 76:145; Fraley et al., *J. Biol. Chem.* (1980) 255:10431; Szoka and Papahadjopoulos, *Proc. Natl. Acad. Sci. USA* (1978)  
10 75:145; and Schaefer-Ridder et al., *Science* (1982) 215:166.

The DNA can also be delivered in cochleate lipid compositions similar to those described by Papahadjopoulos et al., *Biochem. Biophys. Acta.* (1975) 394:483-491. See, also, U.S. Patent Nos. 4,663,161 and 4,871,488.

A number of viral based systems have been developed for gene transfer into  
20 mammalian cells. For example, retroviruses provide a convenient platform for gene delivery systems, such as murine sarcoma virus, mouse mammary tumor virus, Moloney murine leukemia virus, and Rous sarcoma virus. A selected gene can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to cells of the subject  
25 either *in vivo* or *ex vivo*. A number of retroviral systems have been described (U.S. Patent No. 5,219,740; Miller and Rosman, *BioTechniques* (1989) 7:980-990; Miller, A.D., *Human Gene Therapy* (1990) 1:5-14; Scarpa et al., *Virology* (1991) 180:849-852; Burns et al., *Proc. Natl. Acad. Sci. USA* (1993) 90:8033-8037; and Boris-Lawrie and Temin, *Cur. Opin. Genet. Develop.* (1993) 3:102-109. Briefly, retroviral gene delivery  
30 vehicles of the present invention may be readily constructed from a wide variety of retroviruses, including for example, B, C, and D type retroviruses as well as spumaviruses and lentiviruses such as FIV, HIV, HIV-1, HIV-2 and SIV (see RNA

Tumor Viruses, Second Edition, Cold Spring Harbor Laboratory, 1985). Such retroviruses may be readily obtained from depositories or collections such as the American Type Culture Collection ("ATCC"; 10801 University Blvd., Manassas, VA 20110-2209), or isolated from known sources using commonly available techniques.

5       A number of adenovirus vectors have also been described, such as adenovirus Type 2 and Type 5 vectors. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham, *J. Virol.* (1986) 57:267-274; Bett et al., *J. Virol.* (1993) 67:5911-5921; Mittereder et al., *Human Gene Therapy* (1994) 5:717-729; Seth et al., *J. Virol.* (1994) 68:933-940; Barr et al., *Gene Therapy* (1994) 1:51-58; Berkner, K.L. *BioTechniques* (1988) 6:616-629; and Rich et al., *Human Gene Therapy* (1993) 4:461-476).

      Molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al., *J. Biol. Chem.* (1993) 268:6866-6869 and Wagner et al., *Proc. Natl. Acad. Sci. USA* (1992) 89:6099-6103, can also be used for gene delivery.

15       Members of the Alphavirus genus, such as but not limited to vectors derived from the Sindbis and Semliki Forest viruses, VEE, will also find use as viral vectors for delivering the gene of interest. For a description of Sindbis-virus derived vectors useful for the practice of the instant methods, see, Dubensky et al., *J. Virol.* (1996) 70:508-  
20   519; and International Publication Nos. WO 95/07995 and WO 96/17072.

      Other vectors can be used, including but not limited to simian virus 40, cytomegalovirus. Bacterial vectors, such as *Salmonella* ssp. *Yersinia enterocolitica*, *Shigella* spp., *Vibrio cholerae*, *Mycobacterium* strain BCG, and *Listeria monocytogenes* can be used. Minichromosomes such as MC and MC1, bacteriophages,  
25   cosmids (plasmids into which phage lambda *cos* sites have been inserted) and replicons (genetic elements that are capable of replication under their own control in a cell) can also be used.

      The expression constructs may also be encapsulated, adsorbed to, or associated with, particulate carriers. Such carriers present multiple copies of a selected molecule  
30   to the immune system and promote trapping and retention of molecules in local lymph nodes. The particles can be phagocytosed by macrophages and can enhance antigen presentation through cytokine release. Examples of particulate carriers include those



derived from polymethyl methacrylate polymers, as well as microparticles derived from poly(lactides) and poly(lactide-co-glycolides), known as PLG. See, e.g., Jeffery et al., *Pharm. Res.* (1993) 10:362-368; and McGee et al., *J. Microencap.* (1996).

5 A wide variety of other methods can be used to deliver the expression constructs to cells. Such methods include DEAE dextran-mediated transfection, calcium phosphate precipitation, polylysine- or polyornithine-mediated transfection, or precipitation using other insoluble inorganic salts, such as strontium phosphate, aluminum silicates including bentonite and kaolin, chromic oxide, magnesium silicate, talc, and the like. Other useful methods of transfection include electroporation,  
10 sonoporation, protoplast fusion, liposomes, peptoid delivery, or microinjection. See, e.g., Sambrook et al., *supra*, for a discussion of techniques for transforming cells of interest; and Felgner, P.L., *Advanced Drug Delivery Reviews* (1990) 5:163-187, for a review of delivery systems useful for gene transfer. One particularly effective method of delivering DNA using electroporation is described in International Publication No.  
15 WO/0045823.

Additionally, biolistic delivery systems employing particulate carriers such as gold and tungsten, are especially useful for delivering the expression constructs of the present invention. The particles are coated with the construct to be delivered and accelerated to high velocity, generally under a reduced atmosphere, using a gun powder  
20 discharge from a "gene gun." For a description of such techniques, and apparatuses useful therefore, see, e.g., U.S. Patent Nos. 4,945,050; 5,036,006; 5,100,792; 5,179,022; 5,371,015; and 5,478,744.

### Compositions

25 The invention also provides compositions comprising the HCV polypeptides or polynucleotides described herein. Such compositions are useful as diagnostics, for example, using the mutant polypeptides (or polynucleotides encoding these polypeptides) in diagnostic reagents. Diagnostics using polypeptides and polynucleotides are known to those of skill in the art.

30 In addition, immunogenic compounds can be prepared from one or more immunogenic polypeptides derived from the polypeptides described herein, for example the  $\Delta$ NS35 polypeptide. The preparation of immunogenic compounds which

contain immunogenic polypeptide(s) as active ingredients is known to one skilled in the art. Typically, such immunogenic compounds are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified, or  
5 the protein encapsulated in liposomes.

Immunogenic and diagnostic compositions of the invention preferably comprise a pharmaceutically acceptable carrier. The carrier should not itself induce the production of antibodies harmful to the host. Pharmaceutically acceptable carriers are well known to those in the art. Such carriers include, but are not limited to, large,  
10 slowly metabolized, macromolecules, such as proteins, polysaccharides such as latex functionalized sepharose, agarose, cellulose, cellulose beads and the like, polylactic acids, polyglycolic acids, polymeric amino acids such as polyglutamic acid, polylysine, and the like, amino acid copolymers, and inactive virus particles.

Pharmaceutically acceptable salts can also be used in compositions of the  
15 invention, for example, mineral salts such as hydrochlorides, hydrobromides, phosphates, or sulfates, as well as salts of organic acids such as acetates, propionates, malonates, or benzoates. Especially useful protein substrates are serum albumins, keyhole limpet hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid, and other proteins well known to those of skill in the art. Compositions  
20 of the invention can also contain liquids or excipients, such as water, saline, glycerol, dextrose, ethanol, or the like, singly or in combination, as well as substances such as wetting agents, emulsifying agents, or pH buffering agents. Liposomes can also be used as a carrier for a composition of the invention, such liposomes are described above.

25 If desired, co-stimulatory molecules which improve immunogen presentation to lymphocytes, such as B7-1 or B7-2, or cytokines such as GM-CSF, IL-2, and IL-12, can be included in a composition of the invention. Optionally, adjuvants can also be included in a composition. Adjuvants which can be used include, but are not limited to:  
(1) aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate,  
30 aluminum sulfate, etc; (2) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59 (PCT Publ. No. WO 90/14837),

containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing various amounts of MTP-PE), formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, MA), (b) SAF, containing 10% Squalene, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-MDP (see below) either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) Ribi<sup>TM</sup> adjuvant system (RAS), (Ribi Immunochem, Hamilton, MT) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox<sup>TM</sup>); (3) saponin adjuvants, such as Stimulon<sup>TM</sup> (Cambridge Bioscience, Worcester, MA) may be used or particles generated therefrom such as ISCOMs (immunostimulating complexes); (4) Complete Freund's Adjuvant (CFA) and Incomplete Freund's Adjuvant (IFA); (5) cytokines, such as interleukins (e.g., IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, *etc.*), interferons (e.g., gamma interferon), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), *etc.*; (6) detoxified mutants of a bacterial ADP-ribosylating toxin such as a cholera toxin (CT), a pertussis toxin (PT), or an *E. coli* heat-labile toxin (LT), particularly LT-K63, LT-R72, CT-S109, PT-K9/G129; see, e.g., WO 93/13302 and WO 92/19265; (7) other substances that act as immunostimulating agents to enhance the effectiveness of the composition; and (8) microparticles with adsorbed macromolecules, as described in copending U.S. Patent Application Serial No. 09/285,855 (filed April 2, 1999) and international Patent Application Serial No. PCT/US99/17308 (filed July 29, 1999). Alum and MF59 are preferred. The effectiveness of an adjuvant can be determined by measuring the amount of antibodies directed against an immunogenic polypeptide containing an HCV antigenic sequence resulting from administration of this polypeptide in immunogenic compounds which are also comprised of the various adjuvants.

As mentioned above, muramyl peptides include, but are not limited to, N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), -acetyl-normuramyl-L-alanyl-D-isoglutamine (CGP 11637, referred to as nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-hydroxyphosphoryloxy)-ethylamine (CGP 19835A, referred to as MTP-PE), *etc.*

Thus, such recombinant or synthetic HCV polypeptides can be used in vaccines and as diagnostics. Further, antibodies raised against these polypeptides can also be used as diagnostics, or for passive immunotherapy. In addition, antibodies to these polypeptides are useful for isolating and identifying HCV particles.

- 5        Native HCV antigens can also be isolated from HCV virions. The virions can be grown in HCV infected cells in tissue culture, or in an infected host.

### **Administration and Delivery**

- 10        The polynucleotide and polypeptide compositions described herein (*e.g.*, immunogenic compounds) may be administered to a subject using any suitable delivery means. Methods of delivering nucleic acids into host cells are discussed above. Further, HCV polynucleotides and/or polypeptides can be administered parenterally, by injection, usually, subcutaneously, intramuscularly, transdermally or transcutaneously. Certain adjuvants, *e.g.* LTK63, LTR72 or PLG formulations, can be administered
- 15        intranasally or orally. Additional formulations which are suitable for other modes of administration include suppositories. For suppositories, traditional binders and carriers can include, for example, polyalkylene glycols or triglycerides; such suppositories can be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%. Other oral formulations include such normally employed excipients
- 20        as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and contain 10%-95% of active ingredient, preferably 25%-70%.

- 25        The polypeptides of the present invention can be formulated into the immunogenic compound as neutral or salt forms. Pharmaceutically acceptable salts include the acid addition salts (formed with free amino groups of the peptide) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids such as acetic, oxalic, tartaric, maleic, and the
- 30        like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric

hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

The immunogenic compounds are administered in a manner compatible with the dosage formulation, and in such amount as will be prophylactically and/or therapeutically effective. The quantity to be administered, which is generally in the range of 5 micrograms to 250 micrograms of polypeptide per dose, depends on the subject to be treated, capacity of the subject's immune system to synthesize antibodies, and the degree of protection desired. Precise amounts of active ingredient required to be administered may depend on the judgment of the practitioner and can be peculiar to each subject.

The immunogenic compound can be given in a single dose schedule, or preferably in a multiple dose schedule. A multiple dose schedule is one in which a primary course of vaccination can be with 1-10 separate doses, followed by other doses given at subsequent time intervals required to maintain and or reenforce the immune response, for example, at 1-4 months for a second dose, and if needed, a subsequent dose(s) after several months. Further, the course of administration may include polynucleotides and polypeptides, together or sequentially (for example, priming with a polynucleotide composition and boosting with a polypeptide composition). The dosage regimen will also, at least in part, be determined by the need of the individual and be dependent upon the judgment of the practitioner.

In certain embodiments, administration of the polynucleotides and polypeptides described herein is used to activate T cells. In addition to the practical advantages of simplicity of construction and modification, administration of polynucleotides encoding mutant NS polypeptides results in the synthesis of a mutant NS polypeptide in the host. Thus, these immunogens are presented to the host immune system with native post-translational modifications, structure, and conformation. The polynucleotides are preferably injected intramuscularly to a large mammal, such as a human, at a dose of 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 5 or 10 mg/kg.

The proteins and/or polynucleotides can be administered either to a mammal which is not infected with an HCV or can be administered to an HCV-infected mammal. The particular dosages of the polynucleotides or fusion proteins in a composition or will depend on many factors including, but not limited to the species,

age, and general condition of the mammal to which the composition is administered, and the mode of administration of the composition. An effective amount of the composition of the invention can be readily determined using only routine experimentation. *In vitro* and *in vivo* models can be employed to identify appropriate  
5 doses. Generally, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 5 or 10 mg will be administered to a large mammal, such as a baboon, chimpanzee, or human. If desired, co-stimulatory molecules or adjuvants can also be provided before, after, or together with the compositions.

#### 10           **Antibodies and Diagnostics**

Antibodies, both monoclonal and polyclonal, which are directed against HCV epitopes are particularly useful in diagnosis, and those which are neutralizing are useful in passive immunotherapy. Monoclonal antibodies, in particular, may be used to raise anti-idiotypic antibodies.

15           Anti-idiotypic antibodies are immunoglobulins which carry an "internal image" of the antigen of the infectious agent against which protection is desired. Techniques for raising anti-idiotypic antibodies are known in the art. See, e.g., Grzych (1985), Nature 316:74; MacNamara et al. (1984), Science 226:1325, Uytdehaag et al (1985), J. Immunol. 134:1225. These anti-idiotypic antibodies may also be useful for treatment  
20 and/or diagnosis of NANBH, as well as for an elucidation of the immunogenic regions of HCV antigens.

          An immunoassay for viral antigen may use, for example, a monoclonal antibody directed towards a viral epitope, a combination of monoclonal antibodies directed  
towards epitopes of one viral polypeptide, monoclonal antibodies directed towards  
25 epitopes of different viral polypeptides, polyclonal antibodies directed towards the same viral antigen, polyclonal antibodies directed towards different viral antigens or a combination of monoclonal and polyclonal antibodies.

          Immunoassay protocols may be based, for example, upon competition, or direct reaction, or sandwich type assays. Protocols may also, for example, use solid supports,  
30 or may be by immunoprecipitation. Most assays involve the use of labeled antibody or polypeptide. The labels may be, for example, fluorescent, chemiluminescent, radioactive, or dye molecules. Assays which amplify the signals from the probe are also

known. Examples of which are assays which utilize biotin and avidin, and enzyme-labeled and mediated immunoassays, such as ELISA assays.

An enzyme-linked immunosorbent assay (ELISA) can be used to measure either antigen or antibody concentrations. This method depends upon conjugation of an enzyme to either an antigen or an antibody, and uses the bound enzyme activity as a quantitative label. To measure antibody, the known antigen is fixed to a solid phase (e.g., a microplate or plastic cup), incubated with test serum dilutions, washed, incubated with anti-immunoglobulin labeled with an enzyme, and washed again. Enzymes suitable for labeling are known in the art, and include, for example, horseradish peroxidase. Enzyme activity bound to the solid phase is measured by adding the specific substrate, and determining product formation or substrate utilization colorimetrically. The enzyme activity bound is a direct function of the amount of antibody bound.

To measure antigen, a known specific antibody is fixed to the solid phase, the test material containing antigen is added, after an incubation the solid phase is washed, and a second enzyme-labeled antibody is added. After washing, substrate is added, and enzyme activity is estimated colorimetrically, and related to antigen concentration.

The HCV fusion proteins, such as NS3 mutant and core fusion proteins, can also be used to produce HCV-specific polyclonal and monoclonal antibodies. HCV-specific polyclonal and monoclonal antibodies specifically bind to HCV antigens.

Polyclonal antibodies can be produced by administering the fusion protein to a mammal, such as a mouse, a rabbit, a goat, or a horse. Serum from the immunized animal is collected and the antibodies are purified from the plasma by, for example, precipitation with ammonium sulfate, followed by chromatography, preferably affinity chromatography. Techniques for producing and processing polyclonal antisera are known in the art.

Monoclonal antibodies directed against HCV-specific epitopes present in the fusion proteins can also be readily produced. Normal B cells from a mammal, such as a mouse, immunized with, e.g., a mutant NS3 polypeptide or NS-core fusion protein can be fused with, for example, HAT-sensitive mouse myeloma cells to produce hybridomas. Hybridomas producing HCV-specific antibodies can be identified using

RIA or ELISA and isolated by cloning in semi-solid agar or by limiting dilution.

Clones producing HCV-specific antibodies are isolated by another round of screening.

Antibodies, either monoclonal and polyclonal, which are directed against HCV epitopes, are particularly useful for detecting the presence of HCV or HCV antigens in a sample, such as a serum sample from an HCV-infected human. An immunoassay for an HCV antigen may utilize one antibody or several antibodies. An immunoassay for an HCV antigen may use, for example, a monoclonal antibody directed towards an HCV epitope, a combination of monoclonal antibodies directed towards epitopes of one HCV polypeptide, monoclonal antibodies directed towards epitopes of different HCV polypeptides, polyclonal antibodies directed towards the same HCV antigen, polyclonal antibodies directed towards different HCV antigens, or a combination of monoclonal and polyclonal antibodies. Immunoassay protocols may be based, for example, upon competition, direct reaction, or sandwich type assays using, for example, labeled antibody. The labels may be, for example, fluorescent, chemiluminescent, or radioactive.

The polyclonal or monoclonal antibodies may further be used to isolate HCV particles or antigens by immunoaffinity columns. The antibodies can be affixed to a solid support by, for example, adsorption or by covalent linkage so that the antibodies retain their immunoselective activity. Optionally, spacer groups may be included so that the antigen binding site of the antibody remains accessible. The immobilized antibodies can then be used to bind HCV particles or antigens from a biological sample, such as blood or plasma. The bound HCV particles or antigens are recovered from the column matrix by, for example, a change in pH.

## 25        **Methods of Eliciting Immune Responses**

HCV-specific T cells that are activated by the above-described polypeptides, expressed *in vivo* or *in vitro* preferably recognize an epitope of an HCV polypeptide such as a mutant NS3 polypeptide, including an epitope of a mutant HCV polypeptide. HCV-specific T cells can be CD8<sup>+</sup> or CD4<sup>+</sup>.

30        HCV-specific CD8<sup>+</sup> T cells preferably are cytotoxic T lymphocytes (CTL) which can kill HCV-infected cells that display NS3, NS4, NS5a, NS5b epitopes complexed with an MHC class I molecule. HCV-specific CD8<sup>+</sup> T cells may also



express interferon- $\gamma$  (IFN- $\gamma$ ). HCV-specific CD8<sup>+</sup> T cells can be detected by, for example, <sup>51</sup>Cr release assays. <sup>51</sup>Cr release assays measure the ability of HCV-specific CD8<sup>+</sup> T cells to lyse target cells displaying an nonstructural (*e.g.*, mutant NS) epitope. HCV-specific CD8<sup>+</sup> T cells which express IFN- $\gamma$  can also be detected by

5 immunological methods, preferably by intracellular staining for IFN- $\gamma$  after *in vitro* stimulation with a mutant NS polypeptide.

HCV-specific CD4<sup>+</sup> cells activated by the above-described polypeptides, expressed *in vivo* or *in vitro*, and combinations of the individual components of these proteins, preferably recognize an epitope of a mutant non-structural polypeptide,

10 including an epitope of a mutant protein, that is bound to an MHC class II molecule on an HCV-infected cell and proliferate in response to stimulating mutant peptides.

HCV-specific CD4<sup>+</sup> T cells can be detected by a lymphoproliferation assay. Lymphoproliferation assays measure the ability of HCV-specific CD4<sup>+</sup> T cells to proliferate in response to an epitope.

15 Mutant NS (or fusions thereof with core, envelope or other viral polypeptides) can be used to activate HCV-specific T cells either *in vitro* or *in vivo*. Activation of HCV-specific T cells can be used, *inter alia*, to provide model systems to optimize CTL responses to HCV and to provide prophylactic or therapeutic treatment against HCV infection. For *in vitro* activation, proteins are preferably supplied to T cells via a

20 plasmid or a viral vector, such as an adenovirus vector, as described above.

Polyclonal populations of T cells can be derived from the blood, and preferably from peripheral lymphoid organs, such as lymph nodes, spleen, or thymus, of mammals that have been infected with an HCV. Preferred mammals include mice, chimpanzees, baboons, and humans. The HCV serves to expand the number of activated HCV-

25 specific T cells in the mammal. The HCV-specific T cells derived from the mammal can then be restimulated *in vitro* by adding HCV epitopic peptides to the T cells. The HCV-specific T cells can then be tested for, *inter alia*, proliferation (*e.g.*, lymphoproliferation assays known in the art), the production of IFN- $\gamma$ , and the ability to lyse target cells displaying HCV NS epitopes *in vitro*.

30

The following examples are meant to illustrate the invention and are not meant to limit it in any way. Those of ordinary skill in the art will recognize modifications within the spirit and scope of the invention as set forth herein.

5

## EXAMPLES

### Example 1: Constructs

pCMV-II: pCMV-II (Figure 7, SEQ ID NO:5) was created to contain the human CMV promoter, enhancer, intron A, polylinker and the bovine growth hormone terminator in a deleted-pUC backbone (Life Technologies).

pT7-HCV: pT7-HCV was created in a polylinker-modified pUC vector to contain full-length HCV cDNA preceded by a synthetic T7 promoter. pT7-HCV also contains the complete 5' UTR and the poly A version of the 3' UTR.

pCMV.ΔNS35: To generate pCMV.ΔNS35 (Figure 5, SEQ ID NO:3), a two step procedure was undertaken. First, a PCR product was generated from pT7-HCV that corresponded to the following: a 5' EcoRI site, followed by the Kozak sequence of ACCATGG; the initiator ATG followed by amino acid #1242 and continuing to the StuI site. Second, the StuI to XbaI fragment from a full-length genomic clone was isolated. The genomic clone consisted of the T7 promoter fused to the full-length HCV cDNA with the poly A version of the 3' end, in a pUC vector. Finally, the EcoRI-StuI and StuI-XbaI fragments were ligated into the pCMV-II expression vector, transformed into HB101 competent cells and plated onto ampicillin (100 µg/ml). Miniprep analyses led to the identification of the desired clone which was amplified on a larger scale using a Quigen Gigaprep kit following the manufacturer's specifications. The resulting clone was named pCMV.ΔNS35 (Figure 5, SEQ ID NO:3).

pd.ΔNS3NS5: As shown schematically in Figure 10, the yeast expression plasmid pd.ΔNS3NS5 (SEQ ID NO:8) was constructed using restriction fragments obtained from the mammalian expression plasmid pCMV.KM.ΔNS35. pCMV.KM.ΔNS35 is identical to pCMV.ΔNS35 (Figure 5, SEQ ID NO:3) except that it contains a kanamycin resistance gene in the viral backbone. pCMV.KM.ΔNS35 was digested with EcoRI and NheI to obtain 2895bp EcoRI-NheI fragment. EcoRI-NheI

30

fragment was ligated into pRSET HindIII-NheI subcloning vector with oligos (HE) from HindIII to EcoRI. After sequence verification, pRSETHindIII-NheI #6 was digested with HindIII and NheI to obtain a 2908bp HindIII-NheI fragment.

pCMV.KM.ΔNS35 was linearized with XbaI and ligated with synthetic oligos (XS) from XbaI-SalI. The ligation was digested with NheI and SalI to obtain 2481bp NheI-SalI fragment. The fragment was ligated into pET3a NheI-SalI subcloning vector. After sequence verification, pET3a NheI-SalI #2 was digested with NheI and SalI to obtain a 2481bp NheI-SalI fragment. BamHI-HindIII ADH2/GAPDH promoter fragment was then ligated with HindIII-NheI and NheI-SalI fragments into pBS24.1 BamHI-SalI yeast expression vector.

pd.ΔNS3NS5.PJ; pd.ΔNS3NS5.PJ (Figures 13 and 14; SEQ ID NO:10) was generated to create a "perfect junction" at the 5' and 3' end of the HCV coding region. At the 5' end of pd.ΔNS3NS5, there were 6 extra bases between the yeast ADH2/GAPDH promoter and the ATG of the polypeptide. At the 3' end, there were 52 bases of untranslated sequence between the stop codon of the polypeptide and the α-factor terminator in the yeast expression vector. pd.ΔNS3NS5.PJ was created by digesting pd.ΔNS3NS5 #17 with ScaI and SphI to obtain 4963bp ScaI-SphI fragment. pd.NS5b3011 was digested with SphI and SalI to obtain a 321bp SphI-SalI fragment which gave the "perfect junction" at the 3' end of the polypeptide. The ScaI-SphI and SphI-SalI fragments were ligated into pSP72 HindIII-SalI subcloning vector with synthetic oligos from HindIII-ScaI(HS) for the "perfect junction" at the 5' end.

The region of synthetic sequence in pSP72 HindIII-SalI clone# 6 was verified. pSP72 HindIII-SalI clone#6 was digested with HindIII and BlnI or with BlnI and SalI to obtain 2441bp HindIII-BlnI and 2895bp BlnI-SalI fragments, respectively. The BamHI-HindIII ADH2/GAPDH promoter fragment was ligated to HindIII-BlnI and BlnI-SalI fragments into pBS24.1 BamHI-SalI yeast expression vector.

pd.ΔNS3NS5.PJ.core121RT and pd.ΔNS3NS5.PJ.core173RT were generated and encode HCV core aa 1-121 at the C-terminus of the ΔNS3NS5 polypeptide (designated pd.ΔNS3NS5.PJ.core121RT, SEQ ID NO:12) and core aa 1-173 at the C-terminus of the ΔNS3NS5 polypeptide (designated pd.ΔNS3NS5.PJ.core173RT, SEQ ID NO:14). The core sequence had aa 9 mutated from Lys to Arg and aa 11 mutated

from Asn to Thr, designated as core 121RT or 173RT.

pd.ΔNS3NS5.PJ.core121RT and pd.ΔNS3NS5.PJ.core173RT: To generate pd.ΔNS3NS5.PJ.core121RT (Figure 17, SEQ ID NO:12) and pd.ΔNS3NS5.PJ.core173RT (Figure 18, SEQ ID NO:14). As shown in Figure 16, a  
5 NotI-Sal HCVcore121RT and HCVcore173RT were amplified by PCR, from an *E. coli* expression plasmid, pSODCF2.HCVcore191RT #2. Either the core 121RT Not-SalI PCR product or the core 173RT Not-SalI PCR product were ligated into a pT7Blue2 PstI-SalI subcloning vector with synthetic oligos (PN) from PstI to NotI. After  
10 sequence confirmation, pT7Blue2core121RT clone#9 and pT7Blue2core173RT clone#11 was digested with PstI and SalI to obtain 403bp and 559bp PstI-SalI fragments, respectively, for further cloning.

A 121bp NotI-PstI fragment from pSP72 HindIII-SalI clone #6 was isolated as described above during the cloning of pd.ΔNS3NS5.PJ. NotI-PstI and PstI-SalI fragments were assembled into a vector made by digesting pd.ΔNS3NS5.PJ clone#5  
15 (described above) with NotI and SalI.

ΔNS3NS5 and Core 140 and Core 150: An HCV core epitope was found which elicits CTLs in baboons (HCV core aa 121-135). Since pd.ΔNS3NS5.PJ.core121RT ends right before this potentially important epitope and was expressed better than the longer pd.ΔNS3NS5.PJ.core173RT construct (Example 2), two intermediate constructs  
20 were made which include this epitope, possibly giving intermediate expression levels. The two new constructs fused HCV core aa 1-140 or HCV core aa1-150 to the C terminus of ΔNS3NS5.PJ.

pd.ΔNS3NS5.PJ.core140RT (Figure 21, SEQ ID NO:16) and pd.ΔNS3NS5.PJ.core150RT (Figure 22, SEQ ID NO:18): As shown in Figure 20, a  
25 PstI-SalI HCVcore140RT and a PstI-SalIHCVcore150RT fragment were amplified by PCR from pd.ΔNS3NS5.PJ.core173RT clone #16. Ligate either HCV core PstI-SalI PCR products into pT7Blue2 PstI-SalI subcloning vector. After sequence confirmation, pT7Blue2core140RT clone#22 and pT7Blue2core150RT clone#26 were digested with PstI-SalI to obtain 460bp and 490bp PstI-SalI fragments, respectively, for  
30 further cloning.

A 121bp NotI-PstI fragment was isolated from pSP72 HindIII-SalI clone #6 (as described above during the cloning of pd.ΔNS3NS5.PJ. NotI-PstI and PstI-SalI fragments were assembled into a vector made by digesting pd.ΔNS3NS5.PJ clone#5 (described above) with NotI and SalI.

5

### **Example 2: Protein Expression**

Various of the constructs described herein, encoding HCV-1 ΔNS3 to NS5 antigen (aa 1242-3011), were expressed in yeast. *S. cerevisiae* strain AD3 was transformed with pd.ΔNS3NS5 and checked for expression. A stained protein band at the expected molecular weight of 194 kD was not observed (Figure 12). Strain AD3 was also transformed with pd.ΔNS3NS5.PJ clone #5 and checked for expression. A protein band of the expected molecular weight of 194kD was detected (Figure 15).

Strain AD3 was transformed with pd.ΔNS3NS5.PJ.core121RT clone #6 and pd.ΔNS3NS5.PJ.core173RT clone#15 and checked for expression. Protein bands of the expected molecular weight of 206kD and 210kD, respectively, were observed. Expression levels of the pd.ΔNS3NS5.PJ.core173RT construct were much less than that of the pd.ΔNS3NS5.PJ.core121RT construct. (See Figure19). Thus, there is a correlation of protein expression levels and the length of HCV core.

Strain AD3 were transformed with pd.ΔNS3NS5.PJ.core140RT clone# 29 and pd.ΔNS3NS5.PJ.core150RT clone#35 and checked for expression. Bands of the expected molecular weights of 208kD and 209kD were seen by stain at levels close to those of pd.ΔNS3NS5core173RT (Figure 23).

### **Example 3: Eliciting Immune Responses**

#### **A. Immunization**

To evaluate the immunogenicity of the mutant NS polypeptides, studies using guinea pigs, rabbits, mice, rhesus macaques and/or baboons are performed. The studies are structured as follows: DNA immunization alone (single or multiple); DNA immunization followed by protein immunization (boost); DNA immunization followed by protein immunization; immunization by PLG particles. Immunization is intramuscular or mucosally.

### B. Humoral Immune Response

The humoral immune response is checked in serum specimens from immunized animals with anti-NS antibody ELISAs (enzyme-linked immunosorbent assays) at various times post-immunization. Briefly, serum from immunized animals is screened for antibodies directed against the NS or mutant NS proteins. Wells of ELISA microtiter plates are coated overnight with the selected HCV protein and washed four times; subsequently, blocking is done with PBS-0.2% Tween (Sigma). After removal of the blocking solution, diluted mouse serum is added. Sera are tested at various dilutions. Microtiter plates are washed and incubated with a secondary, peroxidase-coupled anti-mouse IgG antibody (Pierce, Rockford, IL). ELISA plates are washed and 3, 3', 5, 5'-tetramethyl benzidine (TMB; Pierce) is added per well. The optical density of each well is measured. Titers are typically reported as the reciprocal of the dilution of serum that gave a half-maximum optical density (O.D.). Similarly, generation of neutralization of binding (NOB) antibodies can be measured by methods known in the art.

### C. Cellular Immune Response

The frequency of specific cytotoxic T-lymphocytes (CTL) is evaluated by a standard chromium release assay of peptide pulsed Balb/c mouse CD4 cells. Briefly, spleen cells (Effector cells, E) are obtained from the BALB/c mice immunized, cultured, restimulated, and assayed for CTL activity against HCV peptide-pulsed target cells. Cytotoxic activity is measured in a standard  $^{51}\text{Cr}$  release assay.

#### **Example 4: Immunization with PLG-delivered DNA.**

The polylactide-co-glycolide (PLG) polymers are obtained from Boehringer Ingelheim, U.S.A. The PLG polymer is RG505, which has a copolymer ratio of 50/50 and a molecular weight of 65 kDa (manufacturers data). Cationic microparticles with adsorbed DNA are prepared using a modified solvent evaporation process, essentially as described in Singh et al., *Proc. Natl. Acad. Sci. USA* (2000) 97:811-816. Briefly, the microparticles are prepared by emulsifying a 5% w/v polymer solution in methylene chloride with PBS at high speed using an IKA homogenizer. The primary emulsion is

then added to distilled water containing cetyl trimethyl ammonium bromide (CTAB) (0.5% w/v). This results in the formation of a w/o/w emulsion which was stirred at room temperature, allowing the methylene chloride to evaporate. The resulting microparticles are washed in distilled water by centrifugation and freeze dried.

- 5    Following preparation, washing and collection, DNA is adsorbed onto the microparticles by incubating cationic microparticles in a solution of DNA. The microparticles are then separated by centrifugation, the pellet washed with TE buffer and the microparticles are freeze dried, resuspended and administered to animals. Antibody titers are measured by ELISA assays.

10

What is claimed is:

1. An isolated mutant non-structural ("NS") HCV polypeptide comprising a polypeptide having a mutation in the catalytic domain of NS3, wherein said mutation  
5 functionally disrupts the catalytic domain.
2. The polypeptide of claim 1, wherein the mutation comprises a deletion.
3. The polypeptide of claim 1, wherein the mutation comprises a  
10 substitution.
4. The polypeptide of any of claims 1-3, wherein said NS polypeptide comprises NS3, NS4 and NS5.
- 15 5. The polypeptide of any of claims 1-3, wherein said NS polypeptide consists of NS3, NS4 and NS5.
6. The polypeptide of any of claims 1-3, wherein said NS polypeptide consists of NS3 and NS5.  
20
7. The polypeptide of claim 6, wherein NS5 consists of NS5a.
8. The polypeptide of claim 6, wherein NS5 consists of NS5b.
- 25 9. The polypeptide of any of claims 1-3, wherein said NS polypeptide consists of NS3 and NS4.
10. The polypeptide of claim 9, wherein NS4 consists of NS4a.
- 30 11. The polypeptide of claim 9, wherein NS4 consists of NS4b.



12. The polypeptide of claim 4, further comprising a second viral polypeptide that is not NS3, NS4, or NS5 of HCV.

13. The polypeptide of claim 12, wherein the second viral polypeptide  
5 comprises an HCV Core polypeptide ("C"), or fragment thereof.

14. The polypeptide of claim 13, wherein the C polypeptide is truncated.

15. The polypeptide of claim 14, wherein the truncation is at amino acid  
10 121.

16. The polypeptide of claim 12, wherein the polypeptide further comprises an HCV envelope protein ("E").

15 17. The polypeptide of claim 16, wherein the E is E1.

18. The polypeptide of claim 16, wherein the E is E2.

19. A composition comprising  
20 (a) the polypeptide of any one of claims 1-18; and  
(b) a pharmaceutically acceptable excipient.

20. An isolated and purified polynucleotide which encodes the mutant HCV polypeptide according to any one of claims 1-18.

25

21. A composition comprising  
(a) the isolated purified polynucleotide of claim 20; and  
(b) a pharmaceutically acceptable excipient.

30 22. The composition of claim 21, wherein the polynucleotide is DNA.

23. The composition of claim 21, wherein the polynucleotide is in a plasmid.
24. An expression vector comprising the polynucleotide of claim 20.
25. An expression vector comprising the polynucleotide of SEQ ID NO:8.
26. A host cell comprising the polynucleotide of claim 20.
27. The host cell of claim 26, wherein the cell is a yeast cell.
28. The host cell of claim 26, wherein the cell is a mammalian cell.
29. The host cell of claim 26, wherein the cell is an insect cell.
30. The host cell of claim 26, wherein the cell is a plant cell.
31. The host cell of claim 26, wherein the polynucleotide comprises the sequence of SEQ ID NO:8.
32. The polypeptide of claim 1, wherein the polypeptide further comprises SEQ ID NO:9.
33. A method of preparing a mutant NS HCV polypeptide, wherein the method comprises the steps of:
- transforming a host cell with an expression vector according to claim 24, under conditions wherein the polypeptide is expressed; and
  - isolating the polypeptide.

34. The method of claim 33, wherein the host cell is a yeast cell.
35. The method of claim 33, wherein the host cell is a mammalian cell.
- 5 36. The method of claim 33, wherein the host cell is an insect cell.
37. The method of claim 33, wherein the host cell is a plant cell.
38. An antibody that specifically binds to a polypeptide of any of claims 1-  
10 18.
39. The antibody of claim 38, wherein the antibody is a monoclonal  
antibody.
- 15 40. The antibody of claim 38, wherein the antibody is a purified polyclonal  
antibody.
41. A method of eliciting an immune response in a subject, comprising the  
step of administering to the subject a polypeptide of any of claims 1-18.
- 20 42. A method of eliciting an immune response in a subject, comprising the  
step of administering to the subject a polynucleotide of claim 20.

Cloning Scheme for Generating pCMV-NS35

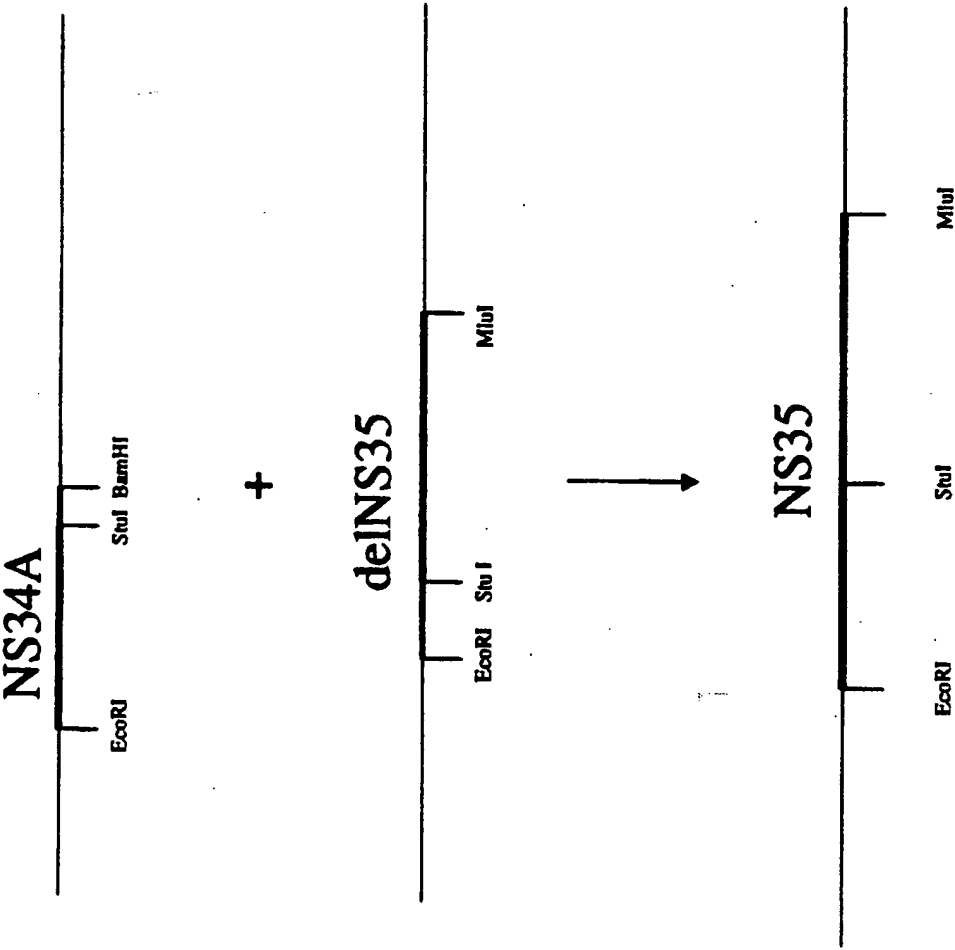
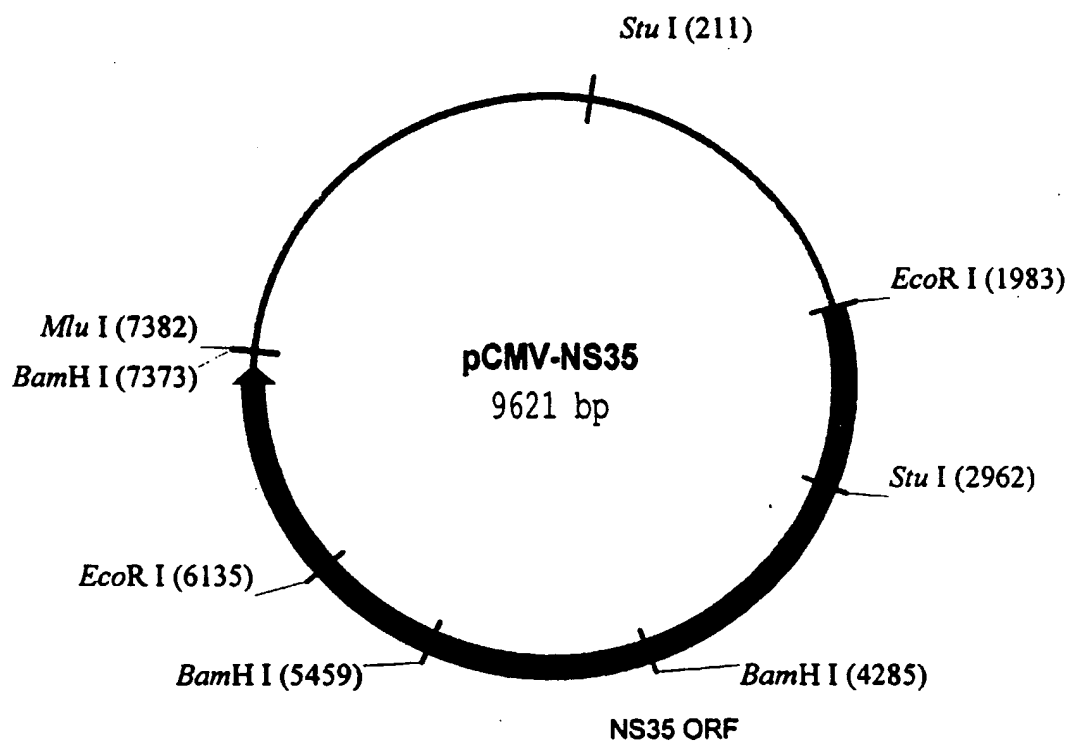


FIGURE 1

FIGURE 2



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## FIGURE 3 - Page 1

1	TCGCGCGTTT	CGGTGATGAC	GGTGAAAACC	TCTGACACAT	GCAGCTCCCG	GAGACGGTCA	CAGCTTGTCT	GTAAGCGGAT
	AGCGCGCAAA	GCCACTACTG	CCACTTTTGG	AGACTGTGTA	CGTCGAGGGC	CTCTGCCAGT	GTCGAACAGA	CATTGCGCTA
81	GCCGGGAGCA	GACAAGCCCC	TCAGGGCGCG	TCAGCGGGTG	TTGGCGGGTG	TCGGGGCTGG	CTTAACATATG	CGGCATCAGA
	CGGCCCTCGT	CTGTTGCGGC	AGTCCCAGCG	AGTCGCCAC	AACCGCCAC	AGCCCCGACC	GAATTGATAC	GCCGTAGTCT
StuI								
161	GCAGATTGTA	CTGAGAGTGC	ACCATATGAA	GCTTTTGGCA	AAAGCCTAGG	CCTCCAAAAA	AGCCTCCTCA	CTACTTCTGG
	CGTCTAACAT	GACTCTCAGC	TGGTATACTT	CGAAAAACGT	TTTCGGATCC	GGAGGTTTTT	TCGGAGGAGT	GATGAAGACC
241	AATAGCTCAG	AGGCCGAGGC	GGCCTCGGCC	TCTGCATAAA	TAAAAAAAT	TAGTCAGCCA	TGGGGCGGAG	AATGGGCGGA
	TTATCGAGTC	TCCGGTCCG	CCGGAGCCGG	AGACGTATTT	ATTTTTTTTA	ATCAGTCGGT	ACCCCGCCTC	TTACCCGCT
321	ACTGGGCGGG	GAGGGAATTA	TTGGCTATTG	GCCATTGCAT	ACGTTGTATC	TATATCATAA	TATGTACATT	TATATTGGCT
	TGACCCGCC	CTCCCTTAAT	AACCGATAAC	CGGTAACTGA	TGCAACATAG	ATATAGTATT	ATACATGTAA	ATATAACCGA
401	CATGTCCAAT	ATGACCGCCA	TGTTGACATT	GATTATTGAC	TAGTTATTAA	TAGTAATCAA	TTACGGGGTC	ATTAGTTTAT
	GTACAGGTTA	TACTGGCGGT	ACAACGTAA	CTAATAACTG	ATCAATAATT	ATCATTAGTT	AATGCCCCAG	TAATCAAGTA
481	AGCCCATATA	TGGAGTTCG	CGTTACATAA	CTTACGGTAA	ATGGCCCCGC	TGGGTGACCG	CCCAACGACC	CCCGCCATT
	TCGGGTATAT	ACCTCAAGGC	GCAATGTATT	GAATGCCATT	TACCGGGCGG	ACCGACTGGC	GGGTGTCTGG	GGGCGGGTAA
561	GACGTCAATA	ATGACGTATG	TTCCCATAGT	AACGCCAATA	GGGACTTTCC	ATTGACGTCA	ATGGGTGGAG	TATTTACGGT
	CTGCAGTTAT	TACTGCATAC	AAGGGTATCA	TTGCGGTTAT	CCCTGAAAGG	TAAGTGCAGT	TACCCACCTC	ATAAATGCCA
641	AAACTGCCCA	CTTGGCAGTA	CATCAAGTGT	ATCATATGCC	AAGTCCGCCC	CCTATTGACG	TCAATGACGG	TAAATGGCCC
	TTTGACGGGT	GAACCGTCAT	GTAGTTCACA	TAGTATACGG	TTCAGGCGGG	GGATAACTGC	AGTTACTGCC	ATTTACGGG
721	GCCTGGCATT	ATGCCCAGTA	CATGACCTTA	CGGGAATTTC	CTACTTGGCA	GTACATCTAC	GTATTAGTCA	TCGCTATTAC
	CGGACCGTAA	TACGGGTGAT	GTAAGTGAAT	GCCTGAAAG	GATGAACCGT	CATGTAGATG	CATAATCAGT	AGCGATAATG
801	CATGGTGATG	CGGTTTTGGC	AGTACACCAA	TGGGCGTGGA	TAGCGGTTTG	ACTCACGGGG	ATTTCCAAGT	CTCCACCCCA
	GTACCACTAC	GCCAAAACCG	TCATGTGGTT	ACCCGCACCT	ATCGCCAAAC	TGAGTGCCCC	TAAAGGTTCA	GAGGTGGGGT
881	TTGACGTCAA	TGGGAGTTTG	TTTTGGCACC	AAAATCAACG	GGACTTTCCA	AAATGTGCTA	ATAACCCCGC	CCGTTTGACG
	AACTGCAGTT	ACCCTCAAAC	AAAACCGTGG	TTTTAGTTGC	CCTGAAAGGT	TTTACAGCAT	TATTGGGGCG	GGGCAACTGC
961	CAAAATGGCG	GTAGGCGTGT	ACGGTGGGAG	GTCTATATAA	GCAGAGCTCG	TTTAGTGAAC	CGTCAGATCG	CCTGGAGACG
	GTTTACCCGC	CATCCGCACA	TGCCACCCTC	CAGATATATT	CGTCTCGAGC	AAATCACTTG	GCAGTCTAGC	GGACCTCTGC
1041	CCATCCACGC	TGTTTTGACC	TCCATAGAAG	ACACCGGGAC	CGATCCAGCC	TCCGCGGCCG	GGAACGGTGC	ATTGGAACGC
	GGTAGGTGCG	ACAAAACCTG	AGGTATCTTC	TGTGGCCCTG	GCTAGGTCGG	AGGCGCCGGC	CCTTGCCACG	TAACCTTGCG
1121	GGATTCCCGG	TGCCAAGAGT	GACGTAAGTA	CCGCCTATAG	ACTCTATAGG	CACACCCCTT	TGGCTCTTAT	GCATGCTATA
	CCTAAGGGGC	ACGGTTCTCA	CTGCATTTCAT	GGCGGATATC	TGAGATATCC	GTGTGGGGAA	ACCGAGAATA	CGTACGATAT
1201	CTGTTTTTGG	CTTGGGGCCT	ATACACCCCC	GCTCCTTATG	CTATAGGTGA	TGGTATAGCT	TAGCCTATAG	GTGTGGGTTA
	GACAAAAACC	GAACCCCGGA	TATGTGGGGG	CGAGGAATAC	GATATCCACT	ACCATATCGA	ATCGGATATC	CACACCCAAT
1281	TTGACCATTA	TTGACCACTC	CCCTATTGGT	GACGATACCT	TCCATTACTA	ATCCATAACA	TGGCTCTTTG	CCACAACAT
	AACTGGTAAT	AACTGGTGAG	GGGATAACCA	CTGCTATGAA	AGGTAATGAT	TAGGTATTGT	ACCGAGAAAC	GGTGTTGATA
1361	CTCTATTGGC	TATATGCCAA	TACTCTGTCC	TTCAGAGACT	GACACGGACT	CTGTATTTTT	ACAGGATGGG	GTCCATTTAT
	GAGATAACCG	ATATACGGTT	ATGAGACAGG	AAGTCTCTGA	CTGTGCCTGA	GACATAAAAA	TGTCCTACCC	CAGGTAATAA

pCMV-NS35

FIGURE 3 - Page 2

1441	TATTTACAAA	TTCACATATA	CAACAACGCC	GTCCCCCGTG	CCCGCAGTTT	TTATTAAACA	TAGCGTGCGA	TCTCCGACAT
	ATAAATGTTT	AAGTGTATAT	GTGTGTGCGG	CAGGGGGCAC	GGCGGTCAAA	AATAATTGT	ATCGCACCT	AGAGGCTGTA
1521	CTCGGGTACG	TGTTCCGGAC	ATGGGCTCTT	CTCCGGTAGC	GGCGGAGCTT	CCACATCCGA	GCCCTGGTCC	CATCCGTCCA
	GAGCCCATGC	ACAAGGCCTG	TACCCGAGAA	GAGGCCATCG	CCGCCTCGAA	GGTGTAGGCT	CGGGACCAGG	GTAGGCAGGT
1601	GCGGCTCATG	GTGCTCGGC	AGCTCCTTGC	TCCTAACAGT	GGAGGCCAGA	CTTAGGCACA	GCACAATGCC	CACCACCACC
	CGCCGAGTAC	CAGCGAGCCG	TCGAGGAACG	AGGATTGTCA	CCTCCGGTCT	GAATCCGTGT	CGTGTTACGG	GTGGTGGTGG
1681	AGTGTGCCGC	ACAAGGCCGT	GGCGGTAGGG	TATGTGTCTG	AAAATGAGCT	CGGAGATTGG	GCTCGCACCT	GGACGCAGAT
	TCACACGGCG	TGTTCCGGCA	CCGCCATCCC	ATACACAGAC	TTTTACTCGA	GCCTCTAACC	CGAGCGTGGA	CCTGCGTCTA
1761	GGAAGACTTA	AGGCAGCGGC	AGAAGAAGAT	GCAGGCAGCT	GAGTTGTGTG	ATTCTGATAA	GAGTCAGAGG	TAATCCCGT
	CCTTCTGAAT	TCCGTGCGCG	TCTTCTTCTA	CGTCCGTCTG	CTCAACAACA	TAAGACTATT	CTCAGTCTCC	ATTGAGGGCA
1841	TGCGGTGCTG	TTAACGGTGG	AGGGCAGTGT	AGTCTGAGCA	GTACTCGTTG	CTGCCGCGCG	CGCCACCAGA	CATAATAGCT
	ACGCCACGAC	AATTGCCACC	TCCCGTCAAC	TCAGACTCGT	CATGAGCAAC	GACGGCGCGC	GCGGTGGTCT	GTATTATCGA
+2								
						EcoRI	M A A	
						~~~~~		
1921	GACAGACTAA	CAGACTGTTT	CTTTCCATGG	GTCTTTTCTG	CAGTCACCGT	CGTCGACCTA	AGAATTACCC	ATGGCTGCAT
	CTGTCTGATT	GTCTGACAAG	GAAAGGTACC	CAGAAAAGAC	GTCAGTGGCA	GCAGCTGGAT	TCTTAAGTGG	TACCGACGTA
+2	Y A A Q	G Y K	V L V L	N P S	V A A	T L G F	G A Y	M S K
2001	ATGCAGCTCA	GGGCTATAAG	GTGCTAGTAC	TCAACCCCTC	TGTTGCTGCA	ACACTGGGCT	TTGGTGCTTA	CATGTCCAAG
	TACGTCGAGT	CCCGATATTC	CACGATCATG	AGTTGGGGAG	ACAACGACGT	TGTGACCCGA	AACCACGAAT	GTACAGGTTT
+2	A H G I	D P N	I R T	G V R T	I T T	G S P	I T Y S	T Y G
2081	GCTCATGGGA	TCGATCCTAA	CATCAGGACC	GGGGTGAGAA	CAATTACCAC	TGGCAGCCCC	ATCAGGTACT	CCACCTACGG
	CGAGTACCCT	AGCTAGGATT	GTAGTCCTGG	CCCCACTCTT	GTTAATGGTG	ACCGTCGGGG	TAGTGCATGA	GGTGGATGCC
+2	K F L	A D G G	C S G	G A Y	D I I I	C D E	C H S	T D A
2161	CAAGTTCCTT	GCGACGGCG	GGTGCTCGGG	GGGCGCTTAT	GACATAATAA	TTTGTGACGA	GTGCCACTCC	ACGGATGCCA
	GTTCAAGGAA	CGGCTGCCGC	CCACGAGCCC	CCCGCGAATA	CTGTATTATT	AAACACTGCT	CACGGTGAGG	TGCCTACGGT
+2	T S I L	G I G	T V L D	Q A E	T A G	A R L V	V L A	T A T
2241	CATCCATCTT	GGGCATTGGC	ACTGTCCTTG	ACCAAGCAGA	GACTGCGGGG	GCGAGACTGG	TTGTGCTCGC	CACCGCCACC
	GTAGGTAGAA	CCCGTAACCG	TGACAGGAAC	TGGTTCGTCT	CTGACGCCCC	CGCTCTGACC	AACACGAGCG	GTGGCGGTGG
+2	P P G S	V T V	P H P	N I E E	V A L	S T T	G E I P	F Y G
2321	CCTCCGGGCT	CCGTCACTGT	GCCCCATCCC	AACATCGAGG	AGGTTGCTCT	GTCCACCACC	GGAGAGATCC	CTTTTACGG
	GGAGGCCCGA	GGCAGTGACA	CGGGGTAGGG	TGTAGCTCC	TCCAACGAGA	CAGGTGGTGG	CCTCTCTAGG	GAAAAATGCC
+2	K A I	P L E V	I K G	G R H	L I F C	H S K	K K C	D E L
2401	CAAGGCTATC	CCCCTCGAAG	TAATCAAGGG	GGGGAGACAT	CTCATCTTCT	GTCATTCAAA	GAAGAAGTGC	GACGAACCTG
	GTTCCGATAG	GGGGAGCTTC	ATTAGTTCCC	CCCCTCTGTA	GAGTAGAAGA	CAGTAAGTTT	CTTCTTCACG	CTGTTGAGC
+2	A A K L	V A L	G I N A	V A Y	Y R G	L D V S	V I P	T S G
2481	CCGCAAGGCT	GGTCGCATTG	GGCATCAATG	CCGTGGCCTA	CTACCGCGGT	CTTGACGTGT	CCGTCAATCC	GACCAGCGGC
	GGCGTTTCGA	CCAGCGTAAC	CCGTAGTTAC	GGCACC GGAT	GATGGCGCCA	GAAGTGCACA	GGCAGTAGGG	CTGGTCGGCG
+2	D V V V	V A T	D A L	M T G Y	T G D	F D S	V I D C	N T C
2561	GATGTTGTCG	TCGTGGCAAC	CGATGCCCTC	ATGACCGGCT	ATACCGGCGA	CTTCGACTCG	GTGATAGACT	GCAATACGTG
	CTACAACAGC	AGCACCGTTG	GCTACGGGAG	TACTGGCCGA	TATGGCCGCT	GAAGCTGAGC	CATACTCTGA	CGTTATGCAC

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## FIGURE 3 - Page 3

+2 V T Q T V D F S L D P T F T I E T I T L P Q D A V S  
 2641 . TGTCACCCAG ACAGTCGATT TCAGCCTTGA CCCTACCTTC ACCATTGAGA CAATCACGCT CCCCCAAGAT GCTGTCTCCC  
 ACAGTGGGTC TGTCAGCTAA AGTCGGAACT GGGATGGAAG TGGTAACTCT GTTAGTGCGA GGGGGTTCTA CGACAGAGGG

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+2 R T Q R R G R T G R G K P G I Y R F V A P G E R P S G  
 2721 GCACTCAACG TCGGGGCAGG ACTGGCAGGG GGAAGCCAGG CATCTACAGA TTGTGGGCAC CGGGGGAGCG CCCCTCCGGC  
 CGTGAGTTGC AGCCCCGTCC TGACCGTCCC CTTTCGGTCC GTAGATGTCT AAACACCGTG GCCCCCTCGG GGGGAGGCGC

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+2 M F D S S V L C E C Y D A G C A W Y E L T P A E T T V  
 2801 ATGTTGCACT CGTCCGTCCT CTGTGAGTGC TATGACGCAG GCTGTGCTTG GTATGAGCTC ACGCCCGCCG AGACTACAGT  
 TACAAGCTGA GCAGGCAGGA GACACTCAGC ATACTCGTTC CGACACGAAC CATACTCGAG TCGGGGCGGC TCTGATGTCA

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+2 R L R A Y M N T P G L P V C Q D H L E F W E G V F T  
 2881 TAGGCTACGA GCGTACATGA ACACCCCGGG GCTTCCCGTG TGCCAGGACC ATCTTGAATT TTGGGAGGGC GTCTTTACAG  
 ATCCGATGCT CGCATGTACT TGTGGGGCCC CGAAGGGCAC ACGGTCCTGG TAGAACTTAA AACCCCTCCG CAGAAATGTC  
 StuI

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+2 G L T H I D A H F L S Q T K Q S G E N L P Y L V A Y Q  
 2961 GCTCACTCA TATAGATGCC CACTTTCTAT CCCAGACAAA GCAGAGTGGG GAGAACCCTT CTTACCTGGT AGCGTACCAA  
 CGGAGTGAGT ATATCTACGG GTGAAAGATA GGGTCTGTTT CGTCTCACCC CTCTTGAAG GAATGGACCA TCGCATGGTT  
 StuI

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+2 A T V C A R A Q A P P P S W D Q M W K C L I R L K P T  
 3041 GCCACCGTGT GCGCTAGGGC TCAAGCCCCT CCCCCATCGT GGGACCAGAT GTGGAAGTGT TTGATTCGCC TCAAGCCCAC  
 CGGTGGCACA CGCGATCCCG AGTTCGGGGA GGGGGTAGCA CCCTGGTCTA CACCTTCACA AACTAAGCGG AGTTCGGGTG

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+2 L H G P T P L L Y R L G A V Q N E I T L T H P V T K  
 3121 CCTCCATGGG CCAACACCCC TGCTATACAG ACTGGGCGCT GTTCAGAATG AAATCACCTT GACGCACCCA GTCACCAAAT  
 GGAGGTACCC GGTGTGGGG ACGATATGTC TGACCCGCGA CAAGTCTTAC TTTAGTGGGA CTGCGTGGGT CAGTGGITTA

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+2 Y I M T C M S A D L E V V T S T W V L V G G V L A A L  
 3201 ACATCATGAC ATGCATGTCG GCCGACCTGG AGGTCGTAC GAGCACCTGG GTGCTCGTTG GCGGCGTCTT GGCTGCTTTG  
 TGTAGTACTG TACGTACAGC CGGCTGGACC TCCAGCAGTG CTCGTGGACC CACGAGCAAC CGCCGAGGA CCGACGAAAC

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+2 A A Y C L S T G C V V I V G R V V L S G K P A I I P D  
 3281 GCCGCGTATT GCCTGTCAAC AGGCTGCGTG GTCATAGTGG GCAGGGTCGT CTGTGTCGGG AAGCCGGCAA TCATACCTGA  
 CGGCGCATAA CGGACAGTTG TCCGACGCAC CAGTATCACC CGTCCCAGCA GAACAGGCCC TTCGGCCGTT AGTATGGAGT

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+2 R E V L Y R E F D E M E E C S Q H L P Y I E Q G M M  
 3361 CAGGGAAGTC CTCTACCGAG AGTTCGATGA GATGGAAGAG TGCTCTCAGC ACTTACCGTA CATCGAGCAA GGGATGATGC  
 GTCCCTTCAG GAGATGGGTC TCAAGCTACT CTACCTTCTC ACGAGAGTCG TGAATGGCAT GTAGCTCGTT CCCTACTACG

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+2 L A E Q F K Q K A I G L L Q T A S R Q A E V I A P A V  
 3441 TCGCCGAGCA GTTCAAGCAG AAGGCCCTCG GCCTCCTGCA GACCGCGTCC CGTCAGGCAG AGGTTATCGC CCCTGCTGTC  
 AGCGGCTCGT CAAGTTCGTC TTCCGGGAGC CGGAGGACGT CTGGCGCAGG GCAGTCCGTC TCCAATAGCG GGGACGACAG

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+2 Q T N W Q K L E T F W A K H M W N F I S G I Q Y L A G  
 3521 CAGACCAACT GGCAAAACT CGAGACCTTC TGGGCGAAGC ATATGTGGAA CTTTCATCAGT GGGATACAAT ACTTGGCGGG  
 GTCTGGTTGA CCGTTTTTGA GCTCTGGAAG ACCCGCTTCG TATACACCTT GAAGTAGTCA CCCTATGTTA TGAACCGCCC

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+2 L S T L P G N P A I A S L M A F T A A V T S P L T T  
 3601 CTTGTCAACG CTGCTGGTA ACCCGCCAT TGCTTCATTG ATGGCTTTTA CAGTGCTGT CACCAGCCCA CTAACCACTA  
 GAACAGTTGC GACGGACCAT TGGGGCGGTA ACGAAGTAAC TACCGAAAAT GTCGACGACA GTGGTCGGGT GATTGGTGAT

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+2 S Q T L L F N I L G G W V A A Q L A A P G A A T A F V  
 3681 GCCAAACCCT CCTCTTCAAC ATATTGGGG GGTGGGTGGC TGCCAGCTC GCGCCCCCG GTGCCGTAC TGCCTTTGTG  
 CGGTTTGGGA GGAGAAGTTG TATAACCCCC CCACCCACCG ACGGGTCGAG CGGCGGGGC CACGGCGATG ACGGAAACAC



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## FIGURE 3 - Page 4

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+2 G A G L A G A A I G S V G L G K V L I D I L A G Y G A
3761 GCGCTGGCT TAGTGGCGC CGCCATCGGC AGTGTGGAC TGGGGAAGGT CCTCATAGAC ATCCTTGACG GGTATGGCGC
    CCGCGACCGA ATCGACCGCG GCGGTAGCCG TCACAACTG ACCCTTCCA GGAGTATCTG TAGGAACGTC CCATACCGCG

+2 G V A G A L V A F K I M S G E V P S T E D L V N L L
3841 GGGCGTGGC GGAGCTCTTG TGGCATTCAA GATCATGAGC GGTGAGGTCC CTCCACGGA GGACCTGGTC AATCTACTGC
    CCGCGACCGC CTCGAGAAC ACCGTAAGTT CTAGTACTCG CCACTCCAGG GGAGGTGCCT CTGGACCAG TTAGATGACG

+2 P A I L S P G A L V V G V V C A A I L R R H V G P G E
3921 GGGCATCTC CTCGCCGGA GCCCTGCTAG TCGGCGTGGT CTGTGCAGCA ATACTGCGCC GGCACGTGG CCCGCGCGAG
    GCGGTAGGA GAGCGGCCT CGGAGCATC AGCGCACCA GACACGTCGT TATGACGCG CCGTGCAACC GGGCCCGCTC

+2 G A V Q W M N R L I A F A S R G N H V S P T H Y V P E
4001 GGGGCAVGC AGTGGATGAA CCGGCTGATA GCCTTCGCCT CCCGGGGGAA CCATGTTTCC CCACGCGACT ACGTGCCGGA
    CCGCGTACG TCACCTACTT GGCGGACTAT CGGAAGCGGA GGGCCCCCTT GGTACAAAGG GGTGCGTGA TGCACGGCTC

+2 S D A A A R V T A I L S S L T V T Q L L R R L H Q W
4081 GAGCATGCA GTCGCCGCG TCACTGCCAT ACTCAGCAGC CTCCTGTAA CCCAGCTCCT GAGGCGACTG CACGAGTGGA
    CTCGCTACGT CGACGGGCGC AGTGACGGA TGAGTCGTCG GAGTGACATT GGTGCGAGGA CTCCGCTGAC GTGGTCACCT

+2 I S S E C T T P C S G S W L R D I W D W I C E V L S D
4161 TAAGCTCGGA GTGTACCACT CCATGCTCCG GTTCCTGGCT AAGGGACATC TGGGACTGGA TATGCGAGGT GTTGAGCGAC
    ATTGAGCCT CACATGGTGA GGTACGAGGC CAAGGACCGA TTCCTGTAG ACCCTGACCT ATACGCTCCA CAATCGCTG

+2 F K T W L K A K L M P Q L P G I P F V S C Q R G Y K G
    BamHI
    ~~~~~
4241 TTTAAGACCT GGCTAAAAGC TAAGCTCATG CCACAGCTGC CTGGGATCCC CTTGTGTGCC TGCCAGCGCG GGTATAAGGG
    AAATTCCTGA CCGATTTTCG ATTCGAGTAC GGTGTCGACG GACCTAGGG GAAACACAGG ACGGTGCGCG CCATATTCCC

+2 V W R G D G I M H T R C H C G A E I T G H V K N G T
4321 GGTCTGGCGA GGGGACGGCA TCATGCACAC TCGCTGCCAC TGTGGAGCTG AGATCACTGG ACATGTCAA AACGGGACGA
    CCAGACCGCT CCCCTGCCGT AGTACGTGTG AGCGACGGTG ACACCTCGAC TCTAGTGACC TGTACAGTT TTGCCCTGCT

+2 M R I V G P R T C R N M W S G T F P I N A Y T T G P C
4401 TGAGGATCGT CGGTCTTAGG ACCTGCAGGA ACATGTGGAG TGGGACCTTC CCATTAATG CCTACACCAC GGGCCCCGTG
    ACTCCTAGCA GCCAGGATCC TGGACGTCT TGTACACCTC ACCCTGGAAG GGGTAATTAC GGATGTGGTG CCCGGGGACA

+2 T P L P A P N Y T F A L W R V S A E E Y V E I R Q V G
4481 ACCCCCCTTC CTGCGCGGAA CTACACGTTT GCGCTATGGA GGTGTCTGTC AGAGGAATAC GTGGAGATAA GGCAGGTGGG
    TGGGGGGAAG GACGCGGCTT GATGTGCAAG CGCGATACCT CCCACAGACG TCTCCTTATG CACCTCTATT CCGTCCACCC

+2 D F H Y V T G M T T D N L K C P C Q V P S P E F F T
4561 GGACTTCCAC TACGTGACGG GTATGACTAC TGACAATCTT AAATGCCCGT GCCAGGTCCC ATCGCCCGAA TTTTTCACAG
    CCGTAAGGTG ATGCATGCC CATACTGATG ACTGTAGAA TTTACGGGCA CGGTCCAGGG TAGCGGGCTT AAAAAGTGTC

+2 E L O G V R L H R F A P P C K P L L R E E V S F R V G
4641 AATTGGACGG GGTGCGCCTA CATAGGTTTG CGCCCCCTG CAAGCCCTTG CTGCGGGAGG AGGTATCATT CAGAGTAGGA
    TTAACCTGCC CCACGCGGAT GTATCCAAAC GCGGGGGGAC GTTCGGGAAC GACGCCCTCC TCCATAGTAA GTCTATCCT

+2 L H E Y P V G S Q L P C E P E P D V A V L T S M L T D
4721 CTCACGAAT ACCCGGTAGG GTCGCAATTA CCTTGCGAGC CCGAACCGGA CGTGGCCGTG TTGACGTCCA TGCTCACTGA
    GAGGTGCTTA TGGGCCATCC CAGCGTTAAT GGAACGCTCG GGCTTGGCTT GCACCGGCAC AACTGCAGGT ACGAGTGACT

+2 P S H I T A E A A G R R L A R G S P P S V A S S S A
4801 TCCCTCCCAT ATAACAGCAG AGGCGGCGG GCGAAGGTTG GCGAGGGGAT CACCCCTC TGTTGGCCAGC TCCTCGGCTA
    AGGGAGGGTA TATTGTCGTC TCCGCGGCC CGCTTCCAAC CGCTCCCTA GTGGGGGAG ACACCGGTG AGGAGCCGAT

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FIGURE 3 - Page 5

+2 S Q L S A P S L K A T C T A N H D S P D A E L I E A N  
 4881 GCCAGCTATC CGCTCCATCT CTCAAGGCAA CTTGCACCGC TAACCATGAC TCCCCTGATG CTGAGCTCAT AGAGGCCAAC  
 CGGTCGATAG GCGAGGTAGA GAGTTCCGTT GAACGTGGCG ATTGGTACTG AGGGGACTAC GACTCGAGTA TCTCCGGTTG

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+2 L L W R Q E M G G N I T R V E S E N K V V I L D S F D  
 4961 CTCCTATGGA GCGAGGAGAT GGGCGGCAAC ATCACCAGGG TTGAGTCAGA AAACAAAGTG GTGATTCTGG ACTCCTTCGA  
 GAGGATACCT CCGTCTCTA CCCGCCGTTG TAGTGGTCCC AACTCAGTCT TTTGTTTCAC CACTAAGACC TGAGGAAGCT

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+2 P L V A E E D E R E I S V P A E I L R K S R R F A Q  
 5041 TCCGCTTGTT GCGGAGGAGG ACGAGCGGGA GATCTCCGTA CCCGCAGAAA TCCTGCGGAA GTCTCGGAGA TTCGCCCAGG  
 AGGCGAACAC CGCTCTCTC TGCTCGCCCT CTAGAGGCAT GGGCGTCTTT AGGACGCCTT CAGAGCCTCT AAGCGGGTCC

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+2 A L P V W A R P D Y N P P L V E T W K K P D Y E P P V  
 5121 CCCTGCCCCG TTGGGCGCGG CCGGACTATA ACCCCCCGCT AGTGGAGACG TGGAAAAAGC CCGACTACGA ACCACTGTG  
 GGGACGGGCA AACC CGCGC GGCCTGATAT TGGGGGGCGA TCACCTCTGC ACCTTTTTCG GGCTGATGCT TGGTGGACAC

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+2 V H G C P L P P P K S P P V P P P R K K R T V V L T E  
 5201 GTCCATGGGT GCGCGCTTCC ACCTCCAAAG TCCCCTCCTG TGCTTCCGCC TCGGAAGAAG CGGACGGTGG TCCTCACTGA  
 CAGGTACCGA CGGGCGAAGG TGGAGGTTTC AGGGGAGGAC ACGGAGGCGG AGCCTTCTTC GCCTGCCACC AGGAGTGACT

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+2 S T L S T A L A E L A T R S F G S S S T S G I T G D  
 5281 ATCAACCTTA TCTACTGCTT TGGCCGAGCT CGCCACCAGA AGCTTTGGCA GCTCCTCAAC TTCCGGCATT ACGGGCGACA  
 TAGTTGGGAT AGATGACGGA ACCGGCTCGA GCGGTGGTCT TCGAAACCGT CGAGGAGTTG AAGGCCGTAA TGCCCGCTGT

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+2 N T T T S S E P A P S G C P P D S D A E S Y S S M P P  
 5361 ATACGACAAC ATCCTCTGAG CCCGCCCTT CTGGCTGCC CCGGACTCC GACGCTGAGT CCTATTCTC CATGCCCCCC  
 TATGCTGTTG TAGGAGACTC GGGCGGGGAA GACCGACGGG GGGGCTGAGG CTGCGACTCA GGATAAGGAG GTACGGGGGG

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+2 L E G E P G D P D L S D G S W S T V S S E A N A E D V  
 BamHI  
 5441 CTGGAGGGGG AGCCTGGGGA TCCGGATCTT AGCGACGGGT CATGGTCAAC GGTCAAGTAGT GAGGCCAACG CGGAGGATGT  
 GACCTCCCCC TCGGACCCCT AGGCCTAGAA TCGCTGCCCA GTACCAGTTG CCAGTCATCA CTCCGGTTGC GCCTCTACA

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+2 V C C S M S Y S W T G A L V T P C A A E E Q K L P I  
 5521 CGTGTGCTGC TCAATGCTT ACTCTGGAC AGGCGCACTC GTCACCCCGT GCGCCGCGGA AGAACAGAAA CTGCCCATCA  
 GCACACGACG AGTTACAGAA TGAGAACCTG TCCGCGTGAG CAGTGGGGCA CGCGGCGCCT TCTGTCTTT GACGGGTAGT

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+2 N A L S N S L L R H H N L V Y S T T S R S A C Q R Q K  
 5601 ATGCACTAAG CAACTCGTTG CTACGTCACC ACAATTGGT GTATTCCACC ACCTCACGCA GTGCTTGCCA AAGGCAGAAG  
 TACGTGATTC GTTGAACAAC GATGCAGTGG TGTTAAACCA CATAAGGTGG TGGAGTGCCT CACGAACGGT TTCCGTCTTC

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+2 K V T F D R L Q V L D S H Y Q D V L K E V K A A A S K  
 5681 AAAGTCACAT TTGACAGACT GCAAGTTCTG GACAGCCATT ACCAGGACGT ACTCAAGGAG GTTAAAGCAG CGGCGTCAAA  
 TTTCAAGTGA AACTGTCTGA CGTTCAAGAC CTGTGCGTAA TGGTCTGCA TGAGTTCCTC CAATTTCTG CCGCAGTTT

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+2 V K A N L L S V E E A C S L T P P H S A K S K F G Y  
 5761 AGTGAAGGCT AACTTGCTAT CCGTAGAGGA AGCTTGACG CTGACGCCCC CACACTCAGC CAAATCCAAG TTTGGTTATG  
 TCACTTCCGA TTGAACGATA GGCATCTCTC TCGAACGTG GACTGCGGGG GTGTGAGTCG GTTAGGTTC AAACCAATAC

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+2 G A K D V R C H A R K A V T H I N S V W K D L L E D N  
 5841 GGGCAAAAGA CGTCCGTTGC CATGCCAGAA AGGCGGTAAC CCACATCAAC TCCGTGTGGA AAGACCTTCT GGAAGACAAT  
 CCCGTTTTCT GCAGGCAACG GTACGGTCTT TCCGGCATTG GGTGATGTTG AGGCACACCT TTCTGGAAGA CCTTCTGTTA

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+2 V T P I D T T I M A K N E V F C V Q P E K G G R K P A  
 5921 GTAACACCAA TAGACTAC CATCATGGCT AAGAAGGAGG TTTTCTGCGT TCAGCCTGAG AAGGGGGGTC GTAAGCCAGC  
 CATGTGGTT ATCTGTGATG GTAGTACCGA TTCTTGCTCC AAAAGACGCA AGTCGGACTC TTCCCCCAG CATTCGGTGC

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FIGURE 3 - Page 6

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+2  R L I V F P D L G V R V C E K M A L Y D V V T K L P
6001  TCGTCTCATC GTGTTCCCGG ATCTGGGCGT GCGCGTGTGC GAAAAGATGG CTTGTACGA CGTGGTTACA AAGCTCCCCT
    AGCAGAGTAG CACAAGGGGC TAGACCCGCA CGCGCACACG CTTTCTACC GAAACATGCT GCACCAATGT TTCAGAGGGG

+2  L A V M G S S Y G F Q Y S P G Q R V E F L V Q A W K S
    EcoRI
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6081  TGGCCGTGAT GGAAGCTCC TACGGATTCC AATACTCACC AGGACAGCGG GTTGAATTCC TCGTGCAAGC GTGGAAGTCC
    ACCGGCACTA CCCTTCGAGG ATGCTAAGG TTATGAGTGG TCCTGTCGCC CAACTTAAGG AGCAGGTTCC CACCTTCAGG

+2  K K T P M G F S Y D T R C F D S T V T E S D I R T E E
6161  AAGAAACCC CAATGGGGTT CTCGTATGAT ACCCGCTGCT TTGACTCCAC AGTCACTGAG AGCGACATCC GTACGGAGGA
    TTCCTTTGGG GTTACCCCAA GAGCATACTA TGGCGACAGA AACTGAGGTG TCAGTGACTC TCGTGTAGG CATGCCCTCT

+2  A I Y Q C C D L D P Q A R V A I K S L T E R L Y V G
6241  GGCAATCTAC CAATGTTGTG ACCTCGACCC CCAAGCCCGC GTGGCCATCA AGTCCCTCAC CGAGAGGCTT TATGTTGGGG
    CGGTAGATG GTTACAACAC TGGAGCTGGG GGTTCGGGCG CACCGTAGT TCAGGGAGTG GCTCTCCGAA ATACAACCC

+2  G P L T N S R G E N C G Y R R C R A S G V L T T S C G
6321  GCCCTCTTAC CAATCAAGG GGGGAGAACT GCGCTATCG CAGGTGCCG GCGAGCGCG TACTGACAC TAGCTGTGGT
    CGGAGAAATG GTTAAGTTCC CCCCTCTGA GCGGATAGC GTCCACGGCG CGCTCGCCG ATGACTGTTG ATCGACACCA

+2  N T L T C Y I K A R A A C R A A G L Q D C T M L V C G
6401  AACACCTCA CTTGTACAT CAGGCCCCG GCAGCCTGTC GAGCCGAGG GCTCCAGGAC TGCACCATGC TCGTGTGTGG
    TTGTGGAGT GAACATGTA GTTCCGGGCC CGTCGGACAG CTCGGCGTCC CGAGGTCCTG ACGTGTACG AGCACACAC

+2  D D L V V I C E S A G V Q E D A A S L R A F T E A M
6481  CGACGACTTA GTCGTTATCT GTGAAAGCG GGGGGTCCAG GAGGACGCG CGAGCCTGAG AGCCTTCAC GAGGCTATGA
    GCTGCTGAAT CAGCAATAGA CACTTTCGCG CCCCAGGTC CTCTGCGCC GCTCGGACTC TCGGAAGTGC ATCCGATAT

+2  T R Y S A P P G D P P Q P E Y D L E L I T S C S S N V
6561  CCAGGTACTC CGCCCCCCT GGGGACCCCG CACAACCAGA ATACGACTTG GAGCTCATAA CATCATGCTC CTCACACGTG
    GGTCCATGAG CGGGGGGGGA CCCCTGGGG GTGTTGTCT TATGCTGAAC CTCGAGTATT GTAGTAGCAG GAGGTTGCAC

+2  S V A H D G A G K R V Y Y L T R D P T T P L A R A A W
6641  TCAGTCGCCC ACGACGGCGC TGGAAAGAGG GTCTACTACT TCACCCGTGA CCTACAACC CCCTCGCGA GAGCTGCGTG
    AGTCAGCGGG TGCTGCCGCG ACCTTCTCC CAGATGATGG AGTGGGCACT GGGATGTTGG GGGGAGCGCT CTCGACGCAC

+2  E T A R H T P V N S W L G N I I M F A P T L W A R M
6721  GGAGACAGCA AGACACACTC CAGTCAATTC CTGGCTAGGC AACATAATCA TGTTTGCCCC CACACTGTGG GCGAGGATGA
    CCTCTGTCTG TCTGTGTGAG GTCAGTTAAG GACCGATCCG TTGTATTAGT ACAAACGGGG GTGTGACACC CGCTCCTACT

+2  I L M T H F F S V L I A R D Q L E Q A L D C E I Y G A
6801  TACTGATGAC CCATTTCTTT AGCGTCCTTA TAGCCAGGGA CCAGCTTGAA CAGGCCCTCG ATTGCGAGAT CTACGGGGCC
    ATGACTACTG GGTAAAGAAA TCGCAGGAAT ATCGGTCCCT GGTGCAACTT GTCCGGGAGC TAACGCTCTA GATGCCCCGG

+2  C Y S I E P L D L P P I I Q R L H G L S A F S L H S Y
6881  TGCTACTCCA TAGAACCCTT GGATCTACCT CCAATCATTC AAAGACTCCA TGGCCTCAGC GCATTTTTCAC TCCACAGTTA
    ACGATGAGGT ATCTTGGTGA CCTAGATGGA GGTTAGTAAG TTTCTGAGGT ACCGGAGTCG CGTAAAGTG AGGTGTCAAT

+2  S P G E I N R V A A C L R K L G V P P L R A W R H R
6961  CTCTCCAGGT GAAATCAATA GGGTGGCCGC ATGCCTCAGA AAAGTTGGGG TACCGCCCTT GCGAGCTTGG AGACACCGGG
    GAGAGGTCCA CTTAGTTAT CCCACCGGCG TACGGAGTCT TTTGAACCCC ATGGCGGGAA CGCTCGAACC TCTGTGGCCC

+2  A R S V R A R L L A R G G R A A I C G K Y L F N W A V
7041  CCCGGAGCGT CCGCGCTAGG CTTCTGGCCA GAGGAGGCGG GGCTGCCATA TGTGGCAAGT ACCTCTTCAA CTGGGCAGTA
    GGGCCTCGCA GGC CGATCC GAAGACCGGT CTCTCCGTC CCGACGGTAT ACACCGTTCA TGGAGAAGTT GACCCGTCAT

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## FIGURE 3 - Page 7

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+2 R T K L K L T P I A A A G O L D L S G W F T A G Y S G
7121 AGAACAAAGC TCAAACTCAC TCCAATAGCG GCCGCTGGCC AGCTGGACTT GTCCGGCTGG TTCACGGCTG GCTACAGCGG
    TCTTGTTCG AGTTTGAGTG AGGTTATCGC CGCGGACCGG TCGACCTGAA CAGGCCGACC AAGTGCCGAC CGATGTGCGC

+2 G D I Y H S V S H A R P R W I W F C L L L L A A G V
7201 GGGAGACATT TATCAGCGG TGTCTCATGC CCGGCCCGCG TGGATCTGGT TTGCTTACT CCTGCTTGCT GCAGGGGTAG
    CCTCTGTAA ATAGTGTGCG ACAGAGTACG GGCCGGGGCG ACCTAGACCA AAACGGATGA GGACGAACGA CGTCCCCATC

+2 G I Y L L P N R
7281 GCATCTACCT CCTCCCCAAC CGATGAAGGT TGGGGTAAAC ACTCCGGCCT AAAAAAAAAA AAAAATCTAG AAAGGCGCGC
    CGTAGATGGA GGAGGGGTG GCTACTTCCA ACCCCATTG TGAGGCCGGA TTTTTTTTTT TTTTGTAGTC TTTCGCGCGC

          BamHI      MluI
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7361 CAAGATATCA AGGATCCACT ACGCGTTAGA GCTCGCTGAT CAGCCTCGAC TGTGCCTTCT AGTTGCCAGC CATCTGTTGT
    GTTCTATAGT TCCTAGGTGA TCGCAATCT CGAGCGACTA GTCCGGAGCTG ACACGGAAGA TCAACGGTCG GTAGACAACA

7441 TTGCCCCCTCC CCCGTGCCTT CTTGACCTT GGAAGGTGCC ACTCCCACTG TCCTTTCCTA ATAAAATGAG GAAATTGCAT
    AACGGGGAGG GGGCACGGAA GGAAGTGGGA CCTTCCACGG TGAGGGTGAC AGGAAAGGAT TATTTTACTC CTTTAACGTA

7521 CGCATTGTCT GAGTAGGTGT CATTCTATTG TGGGGGGTGG GGTGGGGCAG GACAGCAAGG GGGAGGATTG GGAAGACAAT
    GCGTAACAGA CTCATCCACA GTAAGATAAG ACCCCGCCACC CCACCCCGTC CTGTGCTTCC CCTCTCTAAC CTTCTGTGTA

7601 AGCAGGCATG CTGGGGAGCT CTTCCGCTTC CTCGCTCACT GACTCGCTGC GCTCGGTCTG TCGGCTGCGG CGAGCGGTAT
    TCGTCCGTAC GACCCCTCGA GAAGGCGAAG GAGCGAGTGA CTGAGCGACG CGAGCCAGCA AGCCGACGCC GCTCGCCATA

7681 CAGCTCACTC AAAGGCGGTA ATACGGTTAT CCACGGAATC AGGGGATAAC GCAGGAAAGA ACATGTGAGC AAAAGGCCAG
    GTCGAGTGAG TTTCCGCCAT TATGCCAATA GGTGTCTTAG TCCCTATTG CGTCTTTCT TGTACACTCG TTTTCCGGTC

7761 CAAAAGGCCA GGAACCGTAA AAAGGCCGCG TTGCTGGCGT TTTTCCATAG GCTCCGCCCC CTGACGAGC ATCACAAAAA
    GTTTTCCGGT CTTTGGCATT TTTCCGGCGC AACGACCGCA AAAAGGTATC CGAGGCGGGG GGACTGTCTG TAGTGTTTTT

7841 TCGACGCTCA AGTCAGAGGT GCGGAAACCC GACAGGACTA TAAAGATACC AGGCGTTTCC CCTTGGAAGC TCCCTCGTGC
    AGCTGCGAGT TCAGTCTCCA CCGCTTTGGG CTGTCTGAT ATTTCTATGG TCCGCAAAGG GGGACCTTCG AGGGAGCAGC

7921 GCTCTCCTGT TCCGACCCTG CCGCTTACCG GATACCTGTC CGCCTTTCTC CCTTCGGGAA GCGTGGCGCT TTCTCAATGC
    CGAGAGGACA AGGCTGGGAC GGCGAATGGC CTATGGACAG GCGGAAAGAG GGAAGCCCTT CGCACGCGCA AAGAGTTACG

8001 TCACGCTGTA GGTATCTCAG TTCGGTGTAG GTCGTTGCT CCAAGCTGGG CTGTGTGCAC GAACCCCCCG TTCAGCCCGA
    AGTGCGACAT CCATAGAGTC AAGCCACATC CAGCAAGCGA GGTTCGACCC GACACACGTG CTTGGGGGGG AAGTCGGGCT

8081 CCGCTGCGCC TTATCCGGTA ACTATCGTCT TGAGTCCAAC CCGGTAAGAC ACGACTTATC GCCACTGGCA GCAGGCACTG
    GGCGACGCGG AATAGGCCAT TGATAGCAGA ACTCAGGTTG GGCCATTCTG TGCTGAATAG CGGTGACCGT CGTCGGTGAC

8161 GTAACAGGAT TAGCAGAGCG AGGTATGTAG GCGGTGCTAC AGAGTTCTTG AAGTGGTGGC CTAACCTACG CTACACTAGA
    CATTGTCTTA ATCGTCTCGC TCCATACATC CGCCACGATG TCTCAAGAAC TTCACCACCG GATTGATGCC GATGTGATCT

8241 AGGACAGTAT TTGGTATCTG CGCTCTGCTG AAGCCAGTTA CCTTCGGAAA AAGAGTTGGT AGCTCTTGAT CCGGCAAAACA
    TCCTGTCTATA AACCATAGAC GCGAGACGAC TTCGGTCAAT GGAAGCCTTT TTCTCAACCA TCGAGAATA GGCCGTTTGT

8321 AACCACCGCT GGTAGCGGTG GTTTTTTTGT TTGCAAGCAG CAGATTACGC GCAGAAAAAA AGGATCTCAA GAAGATCCTT
    TTGGTGGCGA CCATCGCCAC CAAAAAACA AACGTTCTGTC GTCTAATGCG CGTCTTTTTT TCCTAGAGTT CTTCTAGGAA

8401 TGATCTTTTC TACGGGGTCT GACGCTCAGT GGAACGAAAA CTCACGTAA GGGATTTTGG TCATGAGATT ATCAAAAAGG
    ACTAGAAAAG ATGCCCCAGA CTGCGAGTCA CCTTGCTTTT GAGTGAATT CCCTAAACC AGTACTCTAA TAGTTTTTCC

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## FIGURE 3 - Page 8

8481 ATCTTCACCT AGATCCTTTT AAATTAAAAA TGAAGTTTAA AATCAATCTA AAGTATATAT GAGTAAACTT GGTCTGACAG  
TAGAAGTGGG TCTAGGAAAA TTTAATTTTT ACTTCAAAT TTAGTTAGAT TTCATATATA CTCATTTGAA CCAGACTGTC

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8561 TTACCAATGC TTAATCAGTG AGGCACCTAT CTCAGCGATC TGTCTATTTT GTTCATCCAT AGTTGCCTGA CTCCCCGTGC  
AATGGTTACG AATTAGTCAC TCCGTGGATA GAGTCGCTAG ACAGATAAAG CAAGTAGGTA TCAACGGACT GAGGGGCAGC

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8641 TGTAGATAAC TACGATACGG GAGGGCTTAC CATCTGGCCC CAGTGCTGCA ATGATACCGC GAGACCCACG CTCACCGGCT  
ACATCTATTG ATGCTATGCC CTCCGAATG GTAGACCGGG GTCACGACGT TACTATGGCG CTCTGGGTGC GAGTGGCCGA

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8721 CCAGATTTAT CAGCAATAAA CCAGCCAGCC GGAAGGGCCG AGCGCAGAAG TGGTCCTGCA ACTTTATCCG CCTCCATCCA  
GGTCTAAATA GTCGTTATTT GGTGCGTCCG CCTTCCCGGC TCGCGTCTTC ACCAGGACGT TGAAATAGGC GGAGGTAGGT

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8801 GTCTATTAAT TGTGCGCGG AAGCTAGAGT AAGTAGTTCG CCAGTTAATA GTTTGCGCAA CGTTGTTGCC ATTGCTACAG  
CAGATAATTA ACAACGGGCC TTCGATCTCA TTCATCAAGC GGTCAATTAT CAAACGCGTT GCAACAACGG TAACGATGTC

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8881 GCATCGTGGT GTCACGCTCG TCGTTTGTTA TGGCTTCATT CAGCTCCGGT TCCCAACGAT CAAGGCGAGT TACATGATCC  
CGTAGCACC AAGTGCAGC AGCAAAACCAT ACCGAAGTAA GTCGAGGCCA AGGGTTGCTA GTTCCGCTCA ATGTACTAGG

---

8961 CCCATGTTGT GCAAAAAAGC GGTAGCTCC TTCGGTCTC CGATCGTTGT CAGAAGTAAG TTGGCCGCGC TGTATCACT  
GGGTACAACA CGTTTTTTCG CCAATCGAGG AAGCCAGGAG GCTAGCAACA GTCTTCATTC AACCAGCGTC ACAATAGTGA

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9041 CATGGTTATG GCAGCACTGC ATATTCTCT TACTGTCTAT CCATCCGTAA GATGCTTTTC TGTGACTGGT GAGTACTCAA  
GTACCAATAC CGTCGTGACG TATTAAGAGA ATGACAGTAC GGTAGGCATT CTACGAAAAG ACACGTACCA CTCATGAGTT

---

9121 CCAAGTCATT CTGAGAATAG TGTATGCGGC GACCGAGTTG CTCTTGCCCG GCGTCAATAC GGGATAATAC CGGCCCACAT  
GGTTCAGTAA GACTCTTATC ACATACGCCG CTGGCTCAAC GAGAACGGGC CGCAGTTATG CCCTATTATG GCGCGGTGTA

---

9201 AGCAGAACTT TAAAGTGCT CATCATTGGA AACGTTCTT CGGGGCGAAA ACTCTCAAGG ATCTTACCGC TGTGAGATC  
TCGTCTTGAA ATTTTCACGA GTAGTAACCT TTTGCAAGAA GCCCGCTTT TGAGAGTTCC TAGAATGGCG ACAACTCTAG

---

9281 CAGTTCGATG TAACCCACTC GTGCACCCAA CTGATCTTCA GCATCTTTTA CTTTCACCAG CGTTTCTGGG TGAGCAAAAA  
GTCAAGCTAC ATTTGGGTGAG CACGTGGGTT GACTAGAAGT CGTAGAAAAT GAAAGTGGTC GCAAAGACCC ACTCGTTTTT

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9361 CAGGAAGGCA AAATGCCGCA AAAAAGGGAA TAAGGGCGAC ACGGAAATGT TGAATACTCA TACTCTTCTT TTTCAATAT  
GTCCTTCCGT TTTACGGCGT TTTTCCCTT ATTCCCGCTG TGCCTTTACA ACTTATGAGT ATGAGAAGGA AAAAGTTATA

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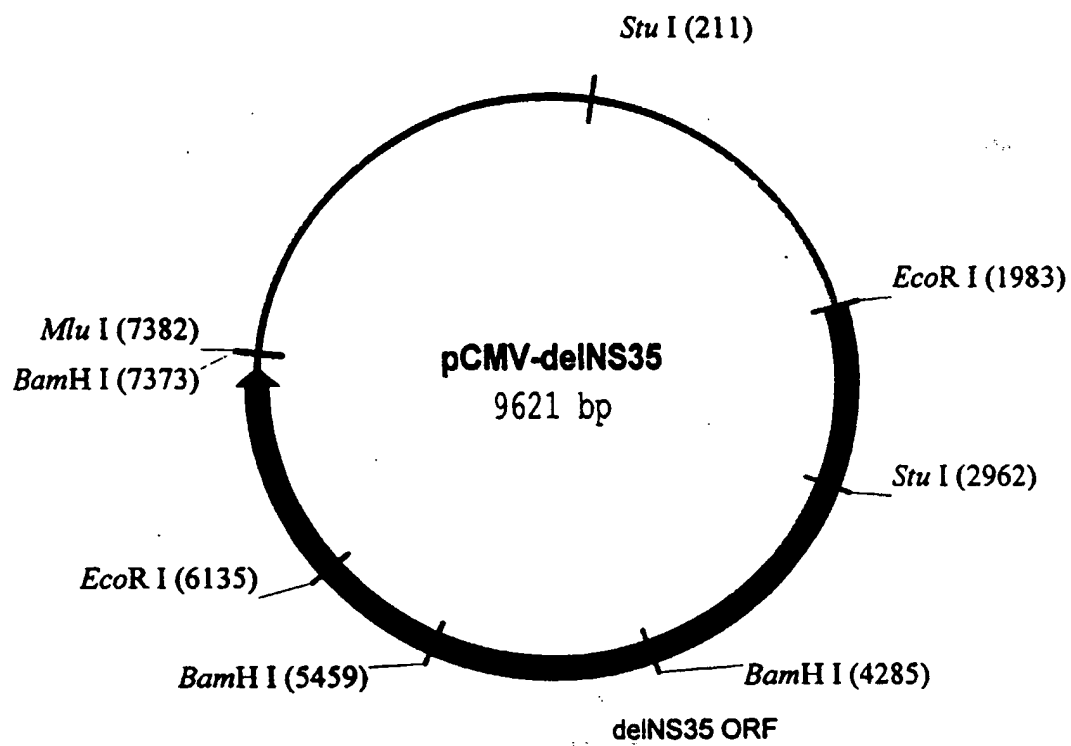
9441 TATTGAAGCA TTTATCAGGG TTATTGCTC ATGAGCGGAT ACATATTTGA ATGTATTTAG AAAAATAAAC AAATAGGGGT  
ATAACTTCGT AAATAGTCCC AATAACAGAG TACTCGCCTA TGTATAAACT TACATAAATC TTTTATTG TTTATCCCA

---

9521 TCCGCGCACA TTTCCCGAA AAGTGCCACC TGACGTCTAA GAAACCATA TTATCATGAC ATTAACCTAT AAAAATAGGC  
AGGCGCGTGT AAAGGGGCTT TTCACGGTGG ACTGCAGATT CTTTGTAAT AATAGTACTG TAATTGGATA TTTTATCCG

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9601 GTATCAGGAG GCCCTTTCGT C  
CATAGTGCTC CGGGAAAGCA G

**FIGURE 4**

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FIGURE 5 - Page 1

1	TCGCGCGTTT	CGGTGATGAC	GGTGAAAACC	TCTGACACAT	GCAGCTCCCG	GAGACGGTCA	CAGCTTGTCT	GTAAGCGGAT
	AGCGCGCAAA	GCCACTACTG	CCACTTTTGG	AGACTGTGTA	CGTCGAGGGC	CTCTGCCAGT	GTCGAACAGA	CATTGCGCTA
81	GCCGGGAGCA	GACAAGCCCG	TCAGGGCGCG	TCAGCGGGTG	TTGGCGGGTG	TCGGGGCTGG	CCTAACTATG	CGGCATCAGA
	CGGCCCTCGT	CTGTTTCGGG	AGTCCCGCGC	AGTCGCCCAC	AACCGCCCAC	AGCCCCGACC	GAATTGATAC	GCCGTAGTCT
StuI -----								
161	GCAGATTGTA	CTGAGAGTGC	ACCATATGAA	GCTTTTTGCA	AAAGCCTAGG	CCTCCAAAAA	AGCCTCCTCA	CTACTTCTGG
	CGTCTAACAT	GACTCTCAGC	TGGTATACTT	CGAAAAACGT	TTTCGGATCC	GGAGGTTTTT	TCGGAGGAGT	GATGAAGACC
241	AATAGCTCAG	AGGCCGAGGC	GGCCTCGGCC	TCTGCATAAA	TAAAAAAAT	TAGTCAGCCA	TGGGGCGGAG	AATGGGCGGA
	TTATCGAGTC	TCCGGCTCCG	CCGGAGCCGG	AGACGTATTT	ATTTTTTTTA	ATCAGTCGGT	ACCCCGCCTC	TTACCCGCTT
321	ACTGGGCGGG	GAGGGAATTA	TTGGCTATTG	GCCATTGCAT	ACGTTGTATC	TATATCATAA	TATGTACATT	TATATTGGCT
	TGACCCGCC	CTCCCTTAAT	AACCGATAAC	CGGTAACGTA	TGCACACATG	ATATAGTATT	ATACATGTAA	ATATAACCGA
401	CATGTCCAAT	ATGACCGCCA	TGTTGACATT	GATTATTGAC	TAGTTATTAA	TAGTAATCAA	TTACGGGGTC	ATTAGTTCAT
	GTACAGGTTA	TACTGGCGGT	ACAACGTGTA	CTAATAACTG	ATCAATAATT	ATCATTAGTT	AATGCCCCAG	TAATCAAGTA
481	AGCCCATATA	TGGAGTTCCG	CGTTACATAA	CTTACGGTAA	ATGGCCCGCC	TGGCTGACCG	CCCAACGACC	CCCGCCCAT
	TGGGTATAT	ACCTCAAGGC	GCAATGTATT	GAATGCCATT	TACCGGGCGG	ACCGACTGGC	GGGTGTCTGG	GGCGGGTAA
561	GACGTCAATA	ATGACGTATG	TTCCCATAGT	AACGCCAATA	GGGACTTTCC	ATTGACGTCA	ATGGGTGGAG	TATTTACGGT
	CTGCAGTTAT	TACTGCATAC	AAGGGTATCA	TTGCGGTAT	CCCTGAAAGG	TAACTGCAGT	TACCCACCTC	ATAAATGCCA
641	AAACTGCCCA	CTTGGCAGTA	CATCAAGTGT	ATCATATGCC	AAGTCCGCCC	CCTATTGACG	TCAATGACGG	TAAATGGCCC
	TTTGACGGGT	GAACCGTCAT	GTAGTTCACA	TAGTATACGG	TTACGGCGGG	GGATAACTGC	AGTTACTGCC	ATTTACCGGG
721	GCCTGGCATT	ATGCCCAGTA	CATGACCTTA	CGGGACTTTC	CTACTTGGCA	GTACATCTAC	GTATTAGTCA	TCGCTATTAC
	CGGACCGTAA	TACGGGTCAT	GTAAGTGAAT	GCCTGAAAG	GATGAACCGT	CATGTAGATG	CATAATCAGT	AGCGATAATG
801	CATGGTGATG	CGGTTTTGGC	AGTACACCAA	TGGGCGTGGA	TAGCGGTTTG	ACTCACGGGG	ATTTCCAAGT	CTCCACCCCA
	GTACCACTAC	GCCAAAACCG	TCATGTGGTT	ACCCGCACCT	ATCGCCAAAC	TGAGTGCCCC	TAAAGGTTCA	GAGGTGGGGT
881	TTGACGTCAA	TGGGAGTTTG	TTTTGGCACC	AAAATCAACG	GGACTTTCCA	AAATGTCGTA	ATAACCCCGC	CCCGTTGACG
	AACTGCAGTT	ACCCTCAAAC	AAAACCGTGG	TTTTAGTTGC	CCTGAAAGGT	TTTACAGCAT	TATTGGGGCG	GGGCAACTGC
961	CAAATGGGCG	GTAGGCGTGT	ACGGTGGGAG	GTCTATATAA	GCAGAGCTCG	TTTAGTGAAC	CGTCAGATCG	CCTGGAGACG
	GTTTACCCGC	CATCCGCACA	TGCCACCCCTC	CAGATATATT	CGTCTCGAGC	AAATCACTTG	GCAGTCTAGC	GGACCTCTGC
1041	CCATCCACGC	TGTTTTGACC	TCCATAGAAG	ACACCGGGAC	CGATCCAGCC	TCCGCGGCGG	GGAACGGTGC	ATTGGAACGC
	GGTAGGTGCG	ACAAAACCTG	AGGTATCTTC	TGTGGCCCTG	GCTAGGTGCG	AGGCGCCGGC	CCTTGCCACG	TAACCTTGCG
1121	GGATTCCCCG	TGCCAAGAGT	GACGTAAGTA	CCGCCTATAG	ACTCTATAGG	CACACCCCTT	TGGCTCTTAT	GCATGCTATA
	CCTAAGGGGC	ACGGTTCTCA	CTGCATTCT	GGCGGATATC	TGAGATATCC	GTGTGGGGAA	ACCGAGARTA	CGTACGATAT
1201	CTGTTTTTGG	CTTGGGGCCT	ATACACCCCC	GTCCTTATG	CTATAGGTGA	TGGTATAGCT	TAGCCTATAG	GIGTGGGTTA
	GACAAAAACC	GAACCCCGGA	TATGTGGGGG	CGAGGAATAC	GATATCCACT	ACCATATCGA	ATCGGATATC	CACACCCAAT
1281	TTGACCATT	TTGACCACTC	CCCTATTGGT	GACGATACTT	TCCATTACTA	ATCCATAACA	TGGCTCTTTG	CCACAACAT
	AACTGGTAAT	AACTGGTGAG	GGGATAACCA	CTGCTATGAA	AGGTAATGAT	TAGGTATTGT	ACCGAGAAAC	GGTGTGATA
1361	CTCTATTGGC	TATATGCCAA	TACTCTGTCC	TTGAGAGACT	GACACGGACT	CTGTATTTT	ACAGGATGGG	GTCCATTAT
	GAGATAACCG	ATATACGGTT	ATGAGACAGG	AAGTCTCTGA	CTGTGCCTGA	GACATAAAAA	TGTCCTACCC	CAGGTAAATA

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## FIGURE 5 - Page 2

1441 TATTTACAAA TTCACATATA CAACAACGCC GTCCCCCGTG CCCGCAGTTT TTATTAAACA TAGCGTGGGA TCTCCGACAT  
ATAAATGTTT AAGTGATAT GTTGTTCGG CAGGGGGCAC GGGCGTCAAA AATAATTTGT ATCGCACCTT AGAGGCTGTA

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1521 CTCGGGTACG TGTTCGGGAC ATGGGCTCTT CTCCGGTAGC GGGCGAGCTT CCACATCCGA GCCCTGGTCC CATCCGTCCA  
GAGCCCATGC ACAAGGCCCTG TACCCGAGAA GAGGCCATCG CCGCCTCGAA GGTGTAGGCT CGGGACCAGG GTAGGCAGGT

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1601 GCGGCTCATG GTCGCTCGGC AGCTCCTTGC TCCTAACAGT GGAGGCCAGA CTTAGGCACA GCACAATGCC CACCACCACC  
CGCCGAGTAC CAGCGAGCCG TCGAGGAACG AGGATTGTCA CCTCCGGTCT GAATCCGTGT CGTGTACCG GTGGTGGTGG

---

1681 AGTGTGCCG ACAAGGCCGT GCGGCTAGGG TATGTGTCTG AAAATGAGCT CGGAGATTGG GCTCGCACCT GGACGCAGAT  
TCACACGGCG TGTTCGGCA CCGCCATCCC ATACACAGAC TTTTACTCGA GCCTCTAACC CGAGCGTGA CCTGCGTCTA

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1761 GGAAGACTTA AGGCAGCGGC AGAAGAAGAT GCAGGCAGCT GAGTGTGTGT ATTCTGATAA GAGTCAGAGG TAACTCCCGT  
CCTTCTGAAT TCCGTGCGCG TCTTCTTCTA CGTCCGTGCA CTCAACAACA TAAGACTATT CTCAGTCTCC ATTGAGGGCA

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1841 TGCGGTGCTG TTAACGGTGG AGGGCAGTGT AGTCTGAGCA GTACTCGTTG CTGCCGCGCG CGCCACCAGA CATAATAGCT  
ACGCCACGAC AATTGCCACC TCCCGTCACA TCAGACTCGT CATGAGCAAC GACGGCGCGC GCGGTGGTCT GTATTATCGA

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+2 M A A  
EcoRI  
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1921 GACAGACTAA CAGACTGTTC CTTTCCATGG GTCTTTTCTG CAGTCACCGT CGTCGACCTA AGAATTCACC ATGGCTGCAT  
CTGTCTGATT GTCTGACAAG GAAAGGTACC CAGAAAAGAC GTCAGTGGCA GCAGCTGGAT TCTTAAGTGG TACCGACGTA

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+2 Y A A Q G Y K V L V L N P S V A A T L G F G A Y M S K

2001 ATGCAGCTCA GGGCTATAAG GTGCTAGTAC TCAACCCCTC TGTGTGTGCA AACTGGGCT TTGGTGTCTA CATGTCCAAG  
TACGTCGAGT CCCGATATTC CACGATCATG AGTTGGGGAG ACAACGACGT TGTGACCCGA AACACGAAT GTACAGGTTC

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+2 A H G I D P N I R T G V R T I T T G S P I T Y S T Y G

2081 GCTCATGGGA TCGATCCTAA CATCAGGACC GGGGTGAGAA CAATTACCAC TGGCAGCCCC ATCAGTACT CCACCTACGG  
CGAGTACCCT AGCTAGGATT GTAGTCTGG CCCCCTCTT GTTAATGGTG ACCGTGCGGG TAGTGATGA GGTGGATGCC

---

+2 K F L A D G G C S G G A Y D I I I C D E C H S T D A

2161 CAAGTTCCTT GCCGACGGCG GTGCTCGGG GGGCGCTTAT GACATAATAA TTTGTGACGA GTGCCACTCC ACCGATGCCA  
GTTCAAGGAA CGGCTGCCGC CCACGAGCCC CCCGGAATA CTGTATTATT AAACACTGCT CACGGTGAGG TGCTACGGT

---

+2 T S I L G I G T V L D Q A E T A G A R L V V L A T A T

2241 CATCCATCTT GGGCATTGGC ACTGTCTTG ACCAAGCAGA GACTGCGGGG GCGAGACTGG TTGTGCTCGC CACCGCCACC  
GTAGGTAGAA CCCGTAACCG TGACAGGAAC TGGTTCGTCT CTGACGCCCC CGCTCTGACC AACACGAGCG GTGGCGGTGG

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+2 P P G S V T V P H P N I E E V A L S T T G E I P F Y G

2321 CCTCCGGGCT CCGTCACTGT GCCCATCCC AACATCGAGG AGGTGTCTCT GTCCACCACC GGAGAGATCC CTTTTACGG  
GGAGGCCCGA GGCAGTGACA CGGGGTAGGG TTGTAGCTCC TCCAACGAGA CAGGTGGTGG CCTCTTAGG GAAAAATGCC

---

+2 K A I P L E V I K G G R H L I F C H S K K K C D E L

2401 CAAGGCTATC CCCCTCGAAG TAATCAAGGG GGGGAGACAT CTCATCTTCT GTCAATCAA GAAGAAGTGC GACGAACCTG  
GTTCCGATAG GGGGAGCTTC ATTAGTTCCT CCCCCTCTGTA GAGTAGAAGA CAGTAAGTTT CTCTTCACG CTGCTTGAGC

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+2 A A K L V A L G I N A V A Y Y R G L D V S V I P T S G

2481 CCGCAAAGCT GGTGCGATTG GGCATCAATG CCGTGGCCTA CTACCGCGGT CTTGACGTGT CCGTCATCCC GACCAGCGGC  
GGCGTTTCGA CCAGCGTAAC CCGTAGTTAC GGCACCGGAT GATGGCGCCA GAAGTGCACA GGCAGTAGGG CTGGTCGCGC

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+2 D V V V V A T D A L M T G Y T G D F D S V I D C N T C

2561 GATGTTGTCG TCGTGGAAC CGATGCCCTC ATGACCGGCT ATACCGGCGA CTTCGACTCG GTGATAGACT GCAATACGTG  
CTACAACAGC AGCACCGTTG GCTACGGGAG TACTGGCCGA TATGGCGGCT GAAGCTGAGC CACTATCTGA CGTTATGCAC



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## FIGURE 5 - Page 3

+2 V T Q T V D F S L D P T F T I E T I T L P Q D A V S  
 2641 TGTCAACCAG ACAGTCGATT TCAGCCTTGA CCCTACCTTC ACCATTGAGA CAATCAGGCT CCCCCAAGAT GCTGTCTCCC  
 ACAGTGGGTC TGTCAGCTAA AGTCGGAAC TGGATGGAAG TGGTAACTCT GTTAGTGCGA GGGGGTTCTA CGACAGAGGG

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+2 R T Q R R G R T G R G K P G I Y R F V A P G E R P S G  
 2721 GCACTCAACG TCGGGGAGG ACTGGCAGGG GGAAGCCAGG CATCTACAGA TTTGTGGCAG CGGGGGAGCG CCCCTCCGGC  
 CGTGAGTTGC AGCCCCGTCC TGACCGTCCC CCTTCGGTCC GTAGATGTCT AAACACCGTG GCCCCTCGC GGGGAGGCGC

---

+2 M F D S S V L C E C Y D A G C A W Y E L T P A E T T V  
 2801 ATGTTCCGACT CGTCCGTCCT CTGTGAGTGC TATGACGAGG GCTGTGCTTG GTATGAGCTC ACGCCCGCCG AGACTACAGT  
 TACAAGCTGA GCAGGCAGGA GACACTCAGC ATACTGCGTC CGACACGAAC CATACTCGAG TCGGGGCGGC TCTGATGTCA

---

+2 R L R A Y M N T P G L P V C Q D H L E F W E G V F T  
 2881 TAGGCTACGA GCGTACATGA ACACCCCGGG GCTTCCCGTG TGCCAGGACC ATCTTGAATT TTGGGAGGGC GTCTTTACAG  
 ATCCGATGCT CGCATGTACT TGTGGGGCCC CGAAGGGCAC ACGGTCTGCG TAGAACTAA AACCTCCCG CAGAAATGTC

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+2 G L T H I D A H F L S Q T K Q S G E N L P Y L V A Y Q  
 2961 GCTCACTCA TATAGATGCC CACTTTCTAT CCCAGACAAA GCAGAGTGGG GAGAACCTTC CTTACCTGGT AGCGTACCAA  
 CGGAGTGAGT ATATCTACGG GTGAAAGATA GGGTCTGTTT CGTCTCAGCC CTCTTGAAG GAATGGACCA TCGCATGGTT

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+2 A T V C A R A Q A P P P S W D Q M W K C L I R L K P T  
 3041 GCCACCGTGT GCGCTAGGGC TCAAGCCCTT CCCCCTATCGT GGGACCAGAT GTGGAAGTGT TTGATTCCGC TCAAGCCAC  
 CCGTGGCACA CGCATCCCG AGTTCGGGGA GGGGGTAGCA CCCTGGTCTA CACCTTACA AACTAAGCGG AGTTCGGGTG

---

+2 L H G P T P L L Y R L G A V Q N E I T L T H P V T K  
 3121 CCTCCATGGG CCAACACCCC TGCTATACAG ACTGGGCGCT GTTCAGAAATG AAATCACCTT GACGCACCCA GTCACCAAAT  
 GGAGGTACCC GGTGTGGGG ACGATATGTC TGACCCGCGA CAAGTCTTAC TTTAGTGGGA CTGCGTGGGT CAGTGGTTTA

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+2 Y I M T C M S A D L E V V T S T W V L V G G V L A A L  
 3201 ACATCATGAC ATGCATGTCG GCCGACCTGG AGGTCGTAC GAGCACCTGG GTGCTCGTTG GCGGCGTCTT GGCTGCTTTG  
 TGTAGTACTG TACGTACAGC CGGCTGGACC TCCAGCAGTG CTGCTGGACC CACGAGCAAC CGCCGAGGA CCGACGAAAC

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+2 A A Y C L S T G C V V I V G R V V L S G K P A I I P D  
 3281 GCCCGGTATT GCCTGTCAAC AGGCTGCGTG GTCATAGTGG GCAGGGTCTG CTGTGTCGGG AAGCCGGCAA TCATACCTGA  
 CGGCGCATAA CGGACAGTTG TCCGACGCAC CAGTATCACC CGTCCCAGCA GAACAGGCCC TTCGGCCGTT AGTATGGACT

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+2 R E V L Y R E F D E M E E C S Q H L P Y I E Q G M M  
 3361 CAGGGAAGTC CTCTACCGAG AGTTCGATGA GATGGAAGAG TGCTCTCAGC ACTTACCGTA CATCGAGCAA GGGATGATGC  
 GTCCCTTCAG GAGATGGCTC TCAAGCTACT CTACCTTCTC ACGAGAGTGC TGAATGGCAT GTAGCTCGTT CCCTACTAGC

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+2 L A E Q F K Q K A L G L L Q T A S R Q A E V I A P A V  
 3441 TCGCCGAGCA GTTCAAGCAG AAGGCCCTCG GCCTCCTGCA GACCGCGTCC CGTCAGGCAG AGGTTATCGC CCCTGCTGTC  
 AGCGGCTCGT CAAGTTCGTC TTCCGGGAGC CGGAGGACGT CTGGCGCAGG GCAGTCCGTC TCCAATAGCG GGGACGACAG

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+2 Q T N W Q K L E T F W A K H M W N F I S G I Q Y L A G  
 3521 CAGACCAACT GGCAAAAAC CGAGACCTTC TGGGCGAAGC ATATGTGGAA CTTCATCAGT GGGATACAAT ACTTGGCGGG  
 GTCTGGTTGA CGTTTTTGA GCTCTGGAAG ACCCGCTTCG TATACACCTT GAAGTAGTCA CCCTATGTGA TGAACCGCCC

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+2 L S T L P G N P A I A S L M A F T A A V T S P L T T  
 3601 CTTGTCAACG CTGCCTGGTA ACCCGCCCAT TGCTTCATTG ATGGCTTTTA CAGCTGCTGT CACCAGCCCA CTAACCACTA  
 GAACAGTTGC GACGGACCAT TGGGGCGGTA ACGAAGTAAC TACCGAAAT GTCGACGACA GTGGTCGGT .GATTGGTGAT

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+2 S Q T L L F N I L G G W V A A Q L A A P G A A T A F V  
 3681 GCCAAACCTT CCTCTTCAAC ATATTGGGGG GGTGGGTGGC TGCCAGCTC GCCGCCCCG GTGCCGCTAC TGCCTTTGGT  
 CGGTTTGGGA GGAGAAGTTG TATAACCCCC CCACCCACCG ACGGGTCGAG CGGCGGGGGC CACGGCGATG ACGGAAACAC

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FIGURE 5 - Page 4

+2 G A G L A G A A I G . S V G L G K V L I D I L A G Y G A  
 3761 . GGCGTGGCT TAGCTGGCGC CGCCATCGGC AGTGTGGAC TGGGGAAGGT CCTCATAGAC ATCCTTGCGAG GGTATGGCGC  
 CCGCGACCGA ATCGACCGCG GCGGTAGCCG TCACAACCTG ACCCCTTCCA GGAGTATCTG TAGGAACGTC CCATACCGCG

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+2 G V A G A L V A F K I M S G E V P S T E D L V N L L  
 3841 . GGGCGTGGCG GGAGCTCTTG TGGCATTCAA GATCATGAGC GGTGAGGTCC CCTCCACGGA GGACCTGGTC AATCTACTGC  
 CCCGACCGC CCTCGAGAAC ACCGTAAGTT CTAGTACTCG CCACTCCAGG GGAGGTGCCT CCTGGACCAG TTAGTGACG

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+2 P A I L S P G A L V V G V V C A A I L R R H V G P G E  
 3921 . CCGCCATCCT CTCGCCCGGA GCCCTCGTAG TCGGCGTGGT CTGTGCAGCA ATACTGCGCC GGCACGTTGG CCCGGGCGAG  
 GGCGGTAGGA GAGCGGGCCT CGGGAGCATC AGCCGCACCA GACACGTCGT TATGACGCGG CCGTGCAACC GGGCCCGCTC

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+2 G A V Q W M N R L I A F A S R G N H V S P T H Y V P E  
 4001 . GGGGCAGTGC AGTGGATGAA CCGGCTGATA GCCTTCGCCT CCCGGGGGAA CCATGTTTCC CCCACGCACT ACGTGCCGGA  
 CCCCGTACG TCACCTACTT GGCCGACTAT CGGAAGCGGA GGGCCCCCTT GGTACAAAGG GGGTCCGTGA TGCACGGCCT

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+2 S D A A A R V T A I L S S L T V T Q L L R R L H Q W  
 4081 . GAGCGATGCA GGTGCCCGCG TCACTGCCAT ACTCAGCAGC CTCACTGTAA CCCAGTCTCT GAGGCGACTG CACCAGTGGA  
 CTCGTACTGT CGACGGGCGC AGTGACGGTA TGAGTCGTCT GAGTGACATT GGGTCGAGGA CTCGCTGAC GTGGTCACTT

---

+2 I S S E C T T P C S G S W L R D I W D W I C E V L S D  
 4161 . TAAGTTCGGA GTGTACCACT CCATGCTCCG GTTCCTGGCT AAGGGACATC TGGGACTGGA TATGCGAGGT GTTGAGCGAC  
 ATTCGAGCCT CACATGGTGA GGTACGAGGC CAAGGACCGA TTCCTGTAG ACCCTGACCT ATACGCTCCA CAACTCGCTG

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+2 F K T W L K A K L M P Q L P G I P F V S C Q R G Y K G  
 BamHI  
 -----  
 4241 . TTTAAGACCT GGCTAAAAGC TAAGCTCATG CCACAGCTGC CTGGGATCCC CTTTGTGTCC TGCCAGCGCG GGTATAAGGG  
 AAATTCTGGA CCGATTTTCG ATTCGAGTAC GGTGTGACG GACCCTAGGG GAAACACAGG ACGGTGCGCG CCATATTCCC

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+2 V W R G D G I M H T R C H C G A E I T G H V K N G T  
 4321 . GGTCTGGCGA GGGGACGGCA TCATGCACAC TCGCTGCCAC TGTGGAGCTG AGATCACTGG ACATGTCAAA AACGGGACGA  
 CGAGACCGCT CCCCTGCCGT AGTACGTGTG AGCGACGGTG ACACCTCGAC TCTAGTGACC TGACAGTTT TTGCCCTGCT

---

+2 M R I V G P R T C R N M W S G T F P I N A Y T T G P C  
 4401 . TGAGGATCGT CGGTCTTAGG ACCTGCAGGA ACATGTGGAG TGGGACCTTC CCCATTAATG CCTACACCAC GGGCCCTGT  
 ACTCTAGCA GCCAGGATCC TGGACGTCTT GTACACCTC ACCCTGGAAG GGGTAATTAC GGATGTGGTG CCCGGGGACA

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+2 T P L P A P N Y T F A L W R V S A E E Y V E I R Q V G  
 4481 . ACCCCCCCTC CTGCGCCGAA CTACACGTTT GCGCTATGGA GGGTGTCTGC AGAGGAATAC GTGGAGATAA GGCAGGTGGG  
 TGGGGGAAG GACGCGGCTT GATGTGCAAG CGCGATACCT CCCACAGAGC TCTCCTTATG CACCTCTATT CCGTCCACCC

---

+2 D F H Y V T G M T T D N L K C P C Q V P S P E F F T  
 4561 . GGACTTCCAC TACGTGACGG GTATGACTAC TGACAATCTT AAATGCCCGT GCCAGGTCCC ATCGCCCGAA TTTTTCACAG  
 CCTGAAGGTG ATGCACTGCC CATACTGATG ACTGTTAGAA TTTACGGGCA CGGTCCAGGG TAGCGGGCTT AAAAGTGTG

---

+2 E L D G V R L H R F A P P C K P L L R E E V S F R V G  
 4641 . AATTGGACGG GGTGCGCCTA CATAGGTTTG CGCCCCCTG CAAGCCCTTG CTGCGGGAGG AGGTATCATT CAGAGTAGGA  
 TTAACCTGCC CCACGCGGAT GTATCCAAAC CGGGGGGAC GTTCGGGAAC GACGCCCTCC TCCATAGTAA GTCTCATCT

---

+2 L H E Y P V G S O L P C E P E P D V A V L T S M L T D  
 4721 . CTCACGAAT ACCCGGTAGG GTCGCAATTA CCTTGCAGC CCGAACCGGA CGTGGCCGTG TTGACGTCCA TGCTCACTGA  
 GAGGTGCTTA TGGGCCATCC CAGCGTTAAT GGAACGCTCG GGCTTGGCCT GCACCGGCAC AACTGCAGGT ACGAGTGACT

---

+2 P S H I T A E A A G R R L A R G S P P S V A S S S A  
 4801 . TCCCTCCCAT ATAACAGCAG AGGCGGCGCG GCGAAGGTTG GCGAGGGGAT CACCCCTCCT TGTGGCCAGC TCCTCGGCTA  
 AGGGAGGGTA TATTGTCGT TCCGCCGCC CGCTTCCAAC CGTCCCTTA GTGGGGGAG ACACCGGTG AGGAGCCGAT

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FIGURE 5 - Page 5

+2 S Q L S A P S L K A T C T A N H D S P D A E L I E A N  
 4881 GCCAGCTATC CGCTCCATCT CTCAAGGCAA CTTCACCGCG TAACCATGAC TCCCTGATG CTGAGCTCAT AGAGGCCAAC  
 CGGTCGATAG GCGAGGTAGA GAGTTCCGTT GAACGTGGCG ATTGGTACTG AGGGGACTAC GACTCGAGTA TCTCCGGTTG

---

+2 L L W R Q E M G G N I T R V E S E N K V V I L D S F D  
 4961 CTCCTATGGA GCGAGGAGAT GGGCGGCAAC ATCACCAGGG TTGAGTCAGA AAACAAAGTG GTGATTCTGG ACTCCTTCGA  
 GAGGATACCT CCGTCTCTA CCCGCCGTTG TAGTGGTCCC AACTCAGTCT TTTGTTTCAC CACTAAGACC TGAGGAAGCT

---

+2 P L V A E E D E R E I S V P A E I L R K S R R F A Q  
 5041 TCCGCTTGTT GCGGAGGAGG ACGAGCGGGA GATCTCCGTA CCCGCAGAAA TCCTGCGGAA GTCTCGGAGA TTCGCCCAGG  
 AGGCGAACAC CGCTCTCTC TGCTCGCCCT CTAGAGGCAT GGGCGTCTTT AGGACGCCTT CAGAGCCTCT AAGCGGGTCC

---

+2 A L P V W A R P D Y N P P L V E T W K K P D Y E P P V  
 5121 CCCTGCCCCG TTGGGCGCGG CCGGACTATA ACCCCCCGCT AGTGGAGACG TGGAAAAAGC CCGACTACGA ACCACCTGTG  
 GGGACGGGCA AACCCGCGCC GGCCTGATAT TGGGGGGCGA TCACCTCTGC ACCTTTTTCG GGCTGATGCT TGGTGGACAC

---

+2 V H G C P L P P P K S P P V P P P R K K R T V V L T E  
 5201 GTCCATGGCT GCGCGCTTCC ACCTCAAAG TCCCTCTCTG TGCCTCCGCC TCGGAAGAAG CCGACGGTGG TCCTCACTGA  
 CAGGTACCGA CGGGCGAAGG TGGAGGTTTC AGGGGAGGAC ACGGAGGCGG AGCCTTCTTC GCCTGCCACC AGGAGTGACT

---

+2 S T L S T A L A E L A T R S F G S S S T S G I T G D  
 5281 ATCAACCCTA TCTACTGCCT TGGCCGAGCT CGCCACCAGA AGCTTTGGCA GCTCCTCAAC TTCGGGCATT ACGGGCGACA  
 TAGTTGGGAT AGATGACGGA ACCGCTCTCA GCGGTGGTCT TCGAAACCGT CGAGGAGTTG AAGGCCGTAA TGCCCGCTGT

---

+2 N T T T S S E P A P S G C P P D S D A E S Y S S M P P  
 5361 ATACGACAAC ATCCTCTGAG CCCGCCCTT CTGGCTGCCC CCCGACTCC GACGCTGAGT CCTATTCTCT CATGCCCCCC  
 TATGCTGTTG TAGGAGACTC GGGCGGGGAA GACCGACGGG GGGGCTGAGG CTGCGACTCA GGATAAGGAG GTACGGGGGG

---

+2 L E G E P G D P D L S O G S W S T V S S E A N A E D V  
 BamHI  
 5441 CTGGAGGGGG AGCCTGGGGA TCCGGATCTT AGCGACGGGT CATGGTCAAC GGTCAGTAGT GAGGCCAACG CGGAGGATGT  
 GACCTCCCCC TCGGACCCCT AGGCCTAGAA TCGCTGCCCA GTACCACTTG CCAGTCATCA CTCCGGTTGC GCCTCTTACA

---

+2 V C C S M S Y S W T G A L V T P C A A E E Q K L P I  
 5521 CGTGTGCTGC TCAATGTCTT ACTCTGGAC AGGCGCACTC GTCACCCCGT GCGCCGCGGA AGAACAGAAA CTGCCCATCA  
 GCACACGACG AGTTACAGAA TGAGAACCTG TCCGCGTGAG CAGTGGGGCA CGCGGCGCCT TCTGTCTTT GACGGGTAGT

---

+2 N A L S N S L L R H H N L V Y S T T S R S A C Q R Q K  
 5601 ATGCACTAAG CAACTCGTTG CTACGTCACC ACAATTGGT GTATTCCACC ACCTCAGCA GTGCTTGCCA AAGGCAGAAG  
 TACGTGATTC GTTGAGCAAC GATGCAGTGG TGTTAAACCA CATAAGGTGG TGGAGTGCCT CACGAACGGT TTCCGTCTTC

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+2 K V T F D R L Q V L D S H Y Q D V L K E V K A A A S K  
 5681 AAAGTCACAT TTGACAGACT GCAAGTTCTG GACAGCCATT ACCAGGACGT ACTCAAGGAG GTTAAAGCAG CGGCGTCAA  
 TTTCAGTGTA AACTGTCTGA CGTTCAAGAC CTGTGCGTAA TGGTCCTGCA TGAGTTCCTC CAATTCGTC GCCCGAGTTT

---

+2 V K A N L L S V E E A C S L T P P H S A K S K F G Y  
 5761 AGTGAAGGCT AACTTGCTAT CCGTAGAGGA AGCTTGCAGC CTGACGCCCC CAACTCAGC CAAATCCAAG TTTGGTTATG  
 TCACCTCCGA TTGAACGATA GGCATCTCT TCGAACGTGC GACTGCGGGG GTGTGAGTCG GTTATAGTTC AAACCAATAC

---

+2 G A K D V R C H A R K A V T H I N S V W K D L L E D N  
 5841 GGGCAAAAGA CGTCCGTTGC CATGCCAGAA AGGCCGTAAC CCACATCAAC TCCGTGTGGA AAGACCTTCT GGAAGACAAT  
 CCCGTTTTCT GCAGGCAACG GTACGGTCTT TCCGGCATTG GGTGATGTTG AGGCACACCT TTCTGGAAGA CTTTCTGTGA

---

+2 V T P I D T T I M A K N E V F C V Q P E K G G R K P A  
 5921 GTAACACCAA TAGACTAC CATCATGGCT AAGAACGAGG TTTTCTGCGT TCAGCCTGAG AAGGGGGGTC GTAAGCCAGC  
 CATTGTGGTT ATCTGTGATG GTAGTACCGA TTCTTGCTCC AAAAGACGCA AGTCGGACTC TTCCCCCAG CATTGGGTGC

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## FIGURE 5 - Page 6

+2 R L I V F P D L G V R V C E K M A L Y D V V T K L P  
6001 TCGTCTCATC GTGTTCCCG ATCTGGCGT GCGCGTGTGC GAAAAGATGG CTTGTACGA CGTGGTTACA AAGCTCCCT  
AGCAGAGTAG CACAAGGGG TAGACCCGCA CGCGCACACG CTTTCTACC GAAACATGCT GCACCAATGT TTCGAGGGGA

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+2 L A V M G S S Y G F Q Y S P G Q R V E F L V Q A W K S  
EcoRI  
~~~~~

6081 TGGCCGTGAT GGGAAAGCTCC TACGGATTCC AATACTCACC AGGACAGCGG GTTGAATTCC TCGTGCAAGC GTGGAAGTCC  
ACCGGCACTA CCCTTCGAGG ATGCCTAAGG TTATGAGTGG TCCTGTGCGC CAACTTAAGG AGCACGTTCC CACCTTCAGG

---

+2 K K T P M G F S Y D T R C F D S T V T E S D I R T E E  
6161 AAGAAAACCC CAATGGGGTT CTCGTATGAT ACCGCTGCT TGGACTCCAC AGTCACTGAG AGCGACATCC GTACGGAGGA  
TTCTTTTGGG GTTACCCCAA GAGCATACTA TGGGCGACGA AACTGAGGTG TCAGTGACTC TCGTGATAGG CATGCCTCT

---

+2 A I Y Q C C D L D P Q A R V A I K S L T E R L Y V G  
6241 GGCATCTAC CAATGTTGT ACCTCGACCC CCAAGCCCGC GTGGCCATCA AGTCCCTCAC CGAGAGGCTT TATGTTGGG  
CCGTTAGATG GTTACAACAC TGGAGCTGGG GGTTCGGGCG CACCGTAGT TCAGGGAGTG GCTCTCCGAA ATACAACCC

---

+2 G P L T N S R G E N C G Y R R C R A S G V L T T S C G  
6321 GCCCTCTTAC CAATCAAGG GGGGAGAACT GCGGCTATCG CAGGTGCCGC GCGAGCGCG TACTGACAAC TAGCTGTGGT  
CGGGAGAATG GTTAAGTTCC CCCCTCTGA CGCGATAGC GTCCAGGCG CGCTCGCCG ATGACTGTTG ATCGACACCA

---

+2 N T L T C Y I K A R A A C R A A G L Q D C T M L V C G  
6401 AACACCTCA CTGTCTACAT CAAGGCCCGG GCAGCCTGTC GAGCCGACG GCTCCAGGAC TGCACCATGC TCGTGTGTGG  
TTGTGGGAGT GAACGATGA GTTCCGGGCC CGTCGGACAG CTCGGCGTCC CGAGGTCTG ACGTGGTACG AGCACACACC

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+2 D D L V V I C E S A G V Q E D A A S L R A F T E A M  
6481 CGACGACTTA GTCGTTATCT GTGAAAGCGC GGGGGTCCAG GAGGACGCGG CGAGCCTGAG AGCCTTCACG GAGGCTATGA  
GCTGCTGAAT CAGCAATAGA CACTTTCGCG CCCCAGGTC CTCCTGCGCC GCTCGGACTC TCGGAAGTGC CTCGGATACT

---

+2 T R Y S A P P G D P P Q P E Y D L E L I T S C S S N V  
6561 CCAGGTACTC CGCCCCCCT GGGGACCCCG CACAACCAGA ATACGACTTG GAGCTCATAA CATCATGCTC CTCCAACGTC  
GGTCCATGAG GCGGGGGGGA CCCCTGGGGG GTGTGGTCT TATGCTGAAC CTCGAGTATT GTAGTACGAG GAGGTTCAC

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+2 S V A H D G A G K R V Y Y L T R D P T T P L A R A A W  
6641 TCAGTCGCCC ACGACGGCGC TGGAAAGAGG GTCTACTACC TCACCCGTGA CCCTACAACC CCCCTCGCGA GAGCTGCGTG  
AGTCAGCGGG TGCTCCGCG ACCTTCTCC CAGATGATGG AGTGGGCACT GGGATGTTGG GGGGAGCGCT CTCGACGCAC

---

+2 E T A R H T P V N S W L G N I I M F A P T L W A R M  
6721 GGAGACAGCA AGACACATC CAGTCAATTC CTGGCTAGGC AACATAATCA TGTTTGCCCC CACTGTGTC GCGAGGATGA  
CCTCTGTCTG TCTGTGTGAG GTCAGTTAAG GACCGATCCG TTGTATTAGT ACAAACGGGG GTGTGACACC CGCTCCTACT

---

+2 I L M T H F F S V L I A R D Q L E Q A L D C E I Y G A  
6801 TACTGATGAC CCATTCTTT AGCGTCTTA TAGCCAGGGA CCAGCTTGAA CAGGCCCTCG ATTGCGAGAT CTACGGGGCC  
ATGACTACTG GGTAAAGAAA TCGCAGGAAT ATCGGTCCTT GGTGCAACTT GTCGGGGAGC TAACGCTCTA GATGCCCGCG

---

+2 C Y S I E P L D L P P I I Q R L H G L S A F S L H S Y  
6881 TGCTACTCCA TAGRACCACT GGATCTACCT CCAATCATC AAAGACTCCA TGGCCTCAGC GCATTTTCAC TCCAGATTA  
ACGATGAGGT ATCTTGGTGA CCTAGATGGA GGTAGTAGG TTTCTGAGGT ACCGGAGTCG CGTAAAAGTG AGGTGTCAAT

---

+2 S P G E I N R V A A C L R K L G V P P L R A W R H R  
6961 CTCTCCAGGT GAAATCAATA GGGTGGCGC ATGCTCAGA AAAGTGGGG TACCGCCCTT GCGAGCTTGG AGACACCGGG  
GAGAGGTCCA CTTTAGTTAT CCCACCGCG TACGGAGTCT TTTGAACCC ATGGCGGGAA CGCTCGAACC TCTGTGCCCC

---

+2 A R S V R A R L L A R G G R A A I C G K Y L E N W A V  
7041 CCGGAGCGT CCGCGCTAGG CTTCTGGCCA GAGGAGGAG GGTGCGCATA TGTGGCAAGT ACCTCTTCAA CTGGGCAGTA  
GGGCTCGCA GCGCGATCC GAAGACCGGT CTCCTCCGTC CCGACGGTAT ACACCGTTCA TGGAGAAGTT GACCCGTCAT

**FIGURE 5 - Page 7**

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**FIGURE 5 - Page 8**

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8481 ATCTTCACCT AGATCCTTTT AAATTAAAAA TGAAGTTTAA AATCAATCTA AAGTATATAT GAGTAAACTT GGTCTGACAG
TAGAAGTGGG TCTAGGAAAA TTAAATTTTT ACTTCAAAAT TTAGTTAGAT TTCATATATA CTCATTTGAA CCAGACTGTC

8561 TTACCAATGC TTAATCAGTG AGGCACCTAT CTCAGCGATC TGTCTATTTT GTTCATCCAT AGTTGCCTGA CTCCCCGTCG
AATGGTTACG AATTAGTCAC TCCGTGGATA GAGTCGCTAG ACAGATAAAG CAAGTAGGTA TCAACGGACT GAGGGGCAGC

8641 TGTAGATAAC TACGATACGG GAGGGCTTAC CATCTGGCCC CAGTGCTGCA ATGATACCGC GAGACCCACG CTCACCGGCT
ACATCTATTG ATGCTATGCC CTCCCGAATG GTAGACCGGG GTCACGACGT TACTATGGCG CTCTGGGTGC GAGTGGCCGA

8721 CCAGATTTAT CAGCAATAAA CCAGCCAGCC GGAAGGGCCG AGCGCAGAAG TGGTCCTGCA ACTTTATCCG CCTCCATCCA
GGTCTAAATA GTCGTTATTT GGTCCGTCCG CCTTCCCGGC TCGCGTCTTC ACCAGGACGT TGAAATAGGC GGAGGTAGGT

8801 GTCTATTAAT TGTTGCCGGG AAGCTAGAGT AAGTAGTTTC CCAGTTAATA GTTTGCGCAA CGTTGTTGCC ATTGCTACAG
CAGATAATTA ACAACGGCCC TTCGATCTCA TTCATCAAGC GGTCAATTAT CAAACGCGTT GCAACAACGG TAACGATGTC

8881 GCATCGTGGT GTCACGCTCG TCGTTTGGA TGGCTTCATT CAGCTCCGGT TOCCAACGAT CAAGGCGAGT TACATGATCC
CGTAGCACCA CAGTGCAGGC AGCAAACCAT ACCGAAGTAA GTCGAGGCCA AGGTTTGCTA GTTCCGCTCA ATGTACTAGG

8961 CCCATGTTGT GCAAAAAAGC GGTTAGCTCC TTCGGTCCCT CGATCGTTGT CAGAAGTAAG TTGGCCGCGAG TGTATCACT
GGGTACAACA CGTTTTTTCG CCAATCGAGG AAGCCAGGAG GCTAGCAACA GTCTTCATTC AACCGCGCTC ACAATAGTGA

9041 CATGGTTATG GCAGCACTGC ATAATTCTCT TACTGTCATG CCATCCGTAA GATGCTTTTC TGTGACTGGT GAGTACTCAA
GTACCAATAC CGTCGTGACG TATTAAGAGA ATGACAGTAC GGTAGGCATT CTACGAAAAG ACACTGACCA CTCATGAGTT

9121 CCAAGTCATT CTGAGAATAG TGTATGCGGC GACCGAGTTG CTCTTGCCCG GCGTCAATAC GGGATAATAC CGCGCCACAT
GGTTCAGTAA GACTCTTATC ACATACGCCG CTGGCTCAAC GAGAACGGGC CGCAGTTATG CCCTATTATG GCGCGGTGTA

9201 AGCAGAACTT TAAAAGTGTCT CATCATTGGA AAACGTTCTT CGGGGCGAAA ACTCTCAAGG ATCTTACCGC TGTGAGATC
TCGTCTTGAA ATTTTCACGA GTAGTAACCT TTTGCAAGAA GCCCGGCTTT TGAGAGTTCC TAGAATGGCG ACAACTCTAG

9281 CAGTTCGATG TAACCCACTC GTGCACCCAA CTGATCTTCA GCATCTTTTA CTTTCACCAG CGTTTCTGGG TGAGCAAAAA
GTCAAGCTAC ATTGGGTGAG CACGTGGGTT GACTAGAAGT CGTAGAAAAT GAAAGTGGTC GCAAAGACCC ACTCGTTTTT

9361 CAGGAAGGCA AAATGCCGCA AAAAAGGGAA TAAGGCGGAC ACGGAAATGT TGAATACTCA TACTCTTCCT TTTTCAATAT
GTCCTTCCGT TTTACGGCGT TTTTCCCTT ATTCCCGCTG TGCCTTTACA ACTTATGAGT ATGAGAAGGA AAAAGTTATA

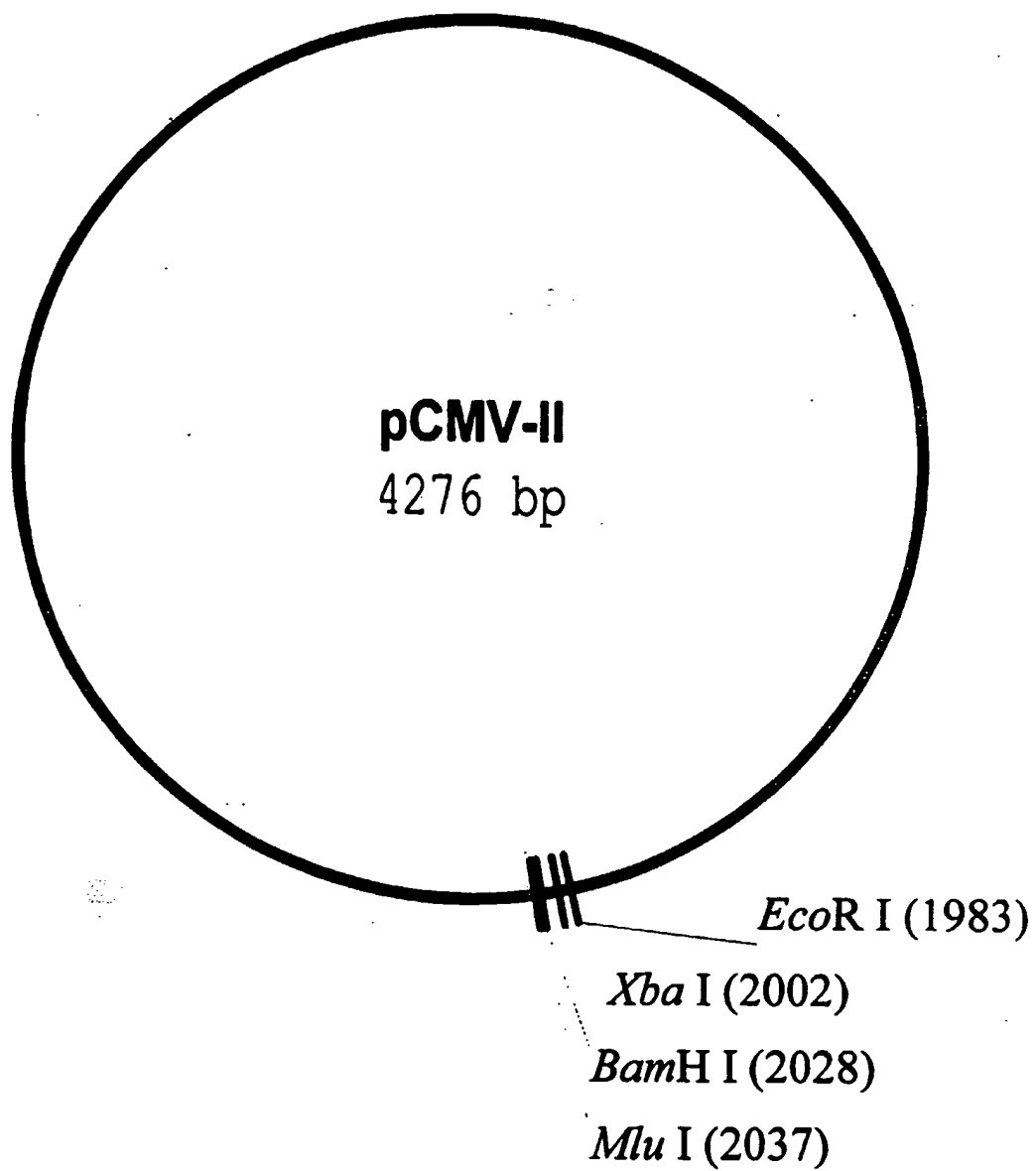
9441 TATTGAAGCA TTTATCAGGG TTATTGTCTC ATGAGCGGAT ACATATTTGA ATGTATTTAG AAAAATAAAC AAATAGGGGT
ATAACTTCGT AAATAGTCCC AATAACAGAG TACTCGCCTA TGTATAAACT TACATAAATC TTTTATTGTT TTTATCCCCA

9521 TCCGCGCACA TTTCCCCGAA AAGTGCCACC TGACGTCTAA GAAACCATTA TTATCATGAC ATTAACCTAT AAAAATAGGC
AGGCGCGTGT AAAGGGGCTT TTCACGGTGG ACTGCAGATT CTTTGTAAT AATAGTACTG TAATTGGATA TTTTATCCG

9601 GTATCAGGAG GCCCTTTCGT C
CATAGTGCTC CGGGAAGCA G

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**FIGURE 6**



## pCMV - II

## FIGURE 7 - Page 1

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1  TCGCGCGTTT CGGTGATGAC GGTGAAAACC TCTGACACAT GCAGCTCCCG GAGACGGTCA CAGCTTGTCT GTAAGCGGAT
   AGCGCGCAAA GCCACTACTG CCACTTTTGG AGACTGTGTA CGTCGAGGGC CTCTGCCAGT GTCGAACAGA CATTCGCCTA

81  GCCGGGAGCA GACAAGCCCG TCAGGGCGCG TCAGCGGGTG TTGGCGGGTG TCGGGGCTGG CTTAACTATG CGGCATCAGA
   CGGCCCTCGT CTGTTCCGGC AGTCCCGCGC AGTCGCCAC AACCGCCAC AGCCCCGACC GAATTGATAC GCCGTAGTCT

161 GCAGATTGTA CTGAGAGTGC ACCATATGAA GCTTTTTGCA AAAGCCTAGG CCTCCAAAAA AGCCTCCTCA CTAATTCTGG
   CGTCTAACAT GACTCTCACG TGGTATACCT CGAAAAACGT TTTCCGGATCC GGAGGTTTTT TCGGAGGAGT GATGAAGACC

241 AATAGCTCAG AGGCCGAGGC GGCCTCGGCC TCTGCATAAA TAAAAAAAT TAGTCAGCCA TGGGGCGGAG AATGGGCGGA
   TTATCGAGTC TCCGGCTCCG CCGGAGCCGG AGACGTATTT ATTTTTTTTA ATCAGTCGGT ACCCCGCTC TTACCCGCTC

321 ACTGGGCGGG GAGGGAATTA TTGGCTATTG GCCATTGCAT ACGTTGTATC TATATCATAA TATGTACATT TATATTGGCT
   TGACCCGCCC CTCCTTAAT AACCGATAAC CGGTAACGTA TGCAACATAG ATATAGTATT ATACATGTAA ATATAACCGA

401 CATGTCCAAT ATGACCGCCA TGTGACATT GATTATTGAC TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTTAT
   GTACAGGTTA TACTGGCGGT ACAACTGTAA CTAATAACTG ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA

481 AGCCCATATA TGGAGTTCGG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG CCCAACGACC CCCGCCCAT
   TCGGGTATAT ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC GGGTTGCTGG GGGCGGGTAA

561 GACGTCAATA ATGACGTATG TTCCCATAGT AACGCCAATA GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTACGGT
   CTGCAGTTAT TACTGCATAC AAGGGTATCA TTGCGGTTAT CCCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

641 AAATGCCCA CTGGCAGTA CATCAAGTGT ATCATATGCC AAGTCCGCCC CCTATTGACG TCAATGACGG TAAATGGCCC
   TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCAGGCGGG GGATAACTGC AGTTACTGCC ATTTACCGGG

721 GCCTGGCATT ATGCCAGTA CATGACCTTA CGGGACTTTC CTACTTGGA GTACATCTAC GTATTAGTCA TCGCTATTAC
   CGGACCGTAA TACGGGTCAT GTACTGGAAT GCCCTGAAAG GATGAACCGT CATGTAGATG CATAATCAGT AGCGATAATG

801 CATGGTGATG CGGTTTTGGC AGTACACCAA TGGCGTGGA TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA
   GTACCACTAC GCCAAAACCG TCATGTGGTT ACCCGCACCT ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT

881 TTGACGTCAA TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA ATAACCCGCG CCCGTTGACG
   AACTGCAGTT ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT TATTGGGGCG GGGCAACTGC

961 CAAATGGGCG GTAGGCGTGT ACGGTGGGAG GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG
   GTTTACCCGC CATCCGCACA TGCCACCTC CAGATATATT CGTCTCGAGC AATCACTTG CGAGTCTAGC GGACCTCTGC

1041 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC TCCGCGGCGG GGAACGGTGC ATTGGAACGC
   GGTAGGTGCG ACAAACCTGG AGGTATCTTC TGTGGCCCTG GCTAGGTCGG AGGCGCCGCG CCTTGCCACG TAACCTTGCG

1121 GGATTCCCCG TGCCAAGAGT GACGTAAGTA CCGCCTATAG ACTCTATAGG CACACCCCTT TGGCTCTTAT GCATGCTATA
   CCTAAGGGGC ACGGTTCTCA CTGCATTCAT GCGGATATC TGAGATATCC GTGTGGGGAA ACCGAGAATA CGTACGATAT

1201 CTGTTTTTGG CTTGGGGCCT ATACACCCCC GCTCCTTATG CTATAGGTGA TGGTATAGCT TAGCCTATAG GTGTGGGTTA
   GACAAAACC GAACCCCGCA TATGTGGGGG CGAGGAATAC GATATCCACT ACCATATCGA ATCGGATATC CACACCCAAT

1281 TTGACCATTA TTGACCACTC CCCTATTGGT GACGATACCT TCCATTACTA ATCCATAACA TGGCTCTTTG CCACAACAT
   AACTGGTAAT AACTGGTGAG GGGATAACCA CTGCTATGAA AGGTAATGAT TAGGTATTGT ACCGAGAAAC GGTGTTGATA

1361 CTCTATTGGC TATATGCCAA TACTCTGTCC TTCAGAGACT GACACGGACT CTGTATTTTT ACAGGATGGG GTCCATTTAT
   GAGATAACCG ATATACGGTT ATGAGACAGG AAGTCTCTGA CTGTGCCTGA GACATAAAAA TGTCCTACCC CAGGTAATAA

1441 TATTACAAA TTCACATATA CAACAACGCC GTCCCGCTG CCGCAGTTT TTATTAAACA TAGCGTGGGA TCTCCGACAT
   ATAAATGTTT AAGTGATAT GTTGTGCGG CAGGGGGCAC GGGCGTCAA AATAATTTGT ATCGCACCTC AGAGGCTGTA

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## pCMV-II

## FIGURE 7 - Page 2

|                                                           |            |             |             |            |            |            |            |            |
|-----------------------------------------------------------|------------|-------------|-------------|------------|------------|------------|------------|------------|
| 1521                                                      | CTCGGGTACG | TGTTCCGGAC  | ATGGGCTCTT  | CTCCGGTAGC | GGCGGAGCTT | CCACATCCGA | GCCCTGGTCC | CATCCGTCCA |
|                                                           | GAGCCCATGC | ACAAGGCCCTG | TACCCGAGAA  | GAGGCCATCG | CCGCCTCGAA | GGTGTAGGCT | CGGGACCAGG | GTAGGCAGGT |
| 1601                                                      | GCGGCTCATG | GTCGCTCGGC  | AGTCCTTGC   | TCCTAACAGT | GGAGGCCAGA | CTTAGGCACA | GCACAATGCC | CACCACCACC |
|                                                           | CGCCGAGTAC | CAGCGAGCCG  | TCGAGGAACG  | AGGATTGTCA | CCTCCGGTCT | GAATCCGTGT | CGTGTACCG  | GTGGTGGTGG |
| 1681                                                      | AGTGTGCCGC | ACAAGGCCGT  | GGCGGTAGGG  | TATGTGTCTG | AAAATGAGCT | CGGAGATTGG | GCTCGCACCT | GGACGCAGAT |
|                                                           | TCACACGGCG | TGTTCCGGCA  | CGCCATCCC   | ATACACAGAC | TTTTACTCGA | GCCTCTAACC | CGAGCGTGGA | CCTGCGTCTA |
| 1761                                                      | GGAAGACTTA | AGGCAGCGGC  | AGAAGAAGAT  | GCAGGCAGCT | GAGTTGTTGT | ATTCTGATAA | GAGTCAGAGG | TAACTCCCGT |
|                                                           | CCTTCTGAAT | TCCGTGCGCG  | TCTTCTTCTA  | CGTCCGTCCA | CTCAACAACA | TAAGACTATT | CTCAGTCTCC | ATTGAGGGCA |
| 1841                                                      | TGCGGTGCTG | TTAACGGTGG  | AGGGCAGTGT  | AGTCTGAGCA | GTACTCGTTG | CTGCCGCGCG | CGCCACCAGA | CATAATAGCT |
|                                                           | ACGCCACGAC | AATTGCCACC  | TCCCGTCACA  | TCAGACTCGT | CATGAGCAAC | GACGGCGCGC | GCGGTGGTCT | GTATTATCGA |
| EcoRI                                                     |            |             |             |            |            |            |            |            |
| 1921                                                      | GACAGACTAA | CAGACTGTTT  | CTTCCATGG   | GTCCTTCTG  | CAGTCACCGT | CGTCGACCTA | AGAATTCAGA | CTCGAGCAAG |
|                                                           | CTGTCTGATT | GTCTGACAAG  | GAAAGGTACC  | CAGAAAAGAC | GTCACTGGCA | GCAGCTGGAT | TCTTAAGTCT | GAGCTCGTTC |
| XbaI                      BamHI                      MluI |            |             |             |            |            |            |            |            |
| 2001                                                      | TCTAGAAAGG | CGCGCCAAGA  | TATCAAGGAT  | CCACTACGCG | TTAGAGCTCG | CTGATCAGCC | TCGACTGTGC | CTTCTAGTTG |
|                                                           | AGATCTTTCC | GCGCGTTTCT  | ATAGTTCCCTA | GGTGATGCGC | AATCTCGAGC | GACTAGTCGG | AGCTGACACG | GAAGATCAAC |
| 2081                                                      | CCAGCCATCT | GTTGTTTGCC  | CCTCCCCCGT  | GCCTTCCTTG | ACCCTGGAAG | GTGCCACTCC | CACTGTCTTT | TCCTAATAAA |
|                                                           | GGTCGGTAGA | CAACAAACGG  | GGAGGGGGCA  | CGGAAGGAAC | TGGGACCTTC | CACGGTGAGG | GTGACAGGAA | AGGATTATTT |
| 2161                                                      | ATGAGGAAAT | TGCATCGCAT  | TGTCTGAGTA  | GGTGTCAATC | TATTCTGGGG | GGTGGGGTGG | GGCAGGACAG | CAAGGGGGAG |
|                                                           | TACTCCTTTA | ACGTAGCGTA  | ACAGACTCAT  | CCACAGTAAG | ATAAGACCCC | CCACCCACC  | CCGTCCTGTC | GTTCCCCCTC |
| 2241                                                      | GATTGGGAAG | ACAATAGCAG  | GCATGCTGGG  | GAGCTCTTCC | GCTTCCTCGC | TCAGTGAATC | GCTGCGCTCG | GTCGTTCCGG |
|                                                           | CTAACCCCTC | TGTTATCGTC  | CGTACGACCC  | CTCGAGAAGG | CGAAGGAGCG | AGTGAATGAG | CGACGCGAGC | CAGCAAGCCG |
| 2321                                                      | TGCGGCGAGC | GGTATCAGCT  | CACTCAAAGG  | CGGTAATACG | GTTATCCACA | GAATCAGGGG | ATAACGCAGG | AAAGAACATG |
|                                                           | ACGCCGCTCG | CCATAGTCGA  | GTGAGTTTCC  | GCCATTATGC | CAATAGGTGT | CTTAGTCCCC | TATTGCGTCC | TTTCTGTGAC |
| 2401                                                      | TGAGCAAAAG | GCCAGCAAAA  | GGCCAGGAAC  | CGTAAAAAGG | CCGCGTTGCT | GGCGTTTTTC | CATAGGCTCC | GCCCCCCTGA |
|                                                           | ACTCGTTTTT | CGGTCGTTTT  | CCGGTCCTTG  | GCATTTTTTC | GGCGCAACGA | CCGCAAAAAG | GTATCCGAGG | CGGGGGGACT |
| 2481                                                      | CGAGCATCAC | AAAAATCGAC  | GCTCAAGTCA  | GAGGTGGCGA | AACCCGACAG | GACTATAAAG | ATACCAGGCG | TTTCCCCCTG |
|                                                           | GCTCGTAGTG | TTTTTAGCTG  | CGAGTTCAGT  | CTCCACCGCT | TTGGGCTGTC | CTGATATTTT | TATGGTCCGC | AAAGGGGGAC |
| 2561                                                      | GAAGCTCCCT | CGTGGCTCT   | CCTGTTCCGA  | CCCTGCCGCT | TACCGGATAC | CTGTCCGCCT | TTCTCCCTTC | GGGAAGCGTG |
|                                                           | CTTCGAGGGA | GCACGCGAGA  | GGACAAGGCT  | GGGACGGCGA | ATGGCCTATG | GACAGGCGGA | AAGAGGGAAG | CCCTTCGCAC |
| 2641                                                      | GCGCTTTCTC | AATGCTCAGG  | CTGTAGGTAT  | CTCAGTTCGG | TGTAGGTCGT | TCGCTCCAAG | CTGGGCTGTG | TGCACGAACC |
|                                                           | CGCGAAAGAG | TTACGAGTGC  | GACATCCATA  | GAGTCAAGCC | ACATCCAGCA | AGCGAGGTTC | GACCCGACAC | ACGTGCTTGG |
| 2721                                                      | CCCCGTTTCA | CCCGACCGCT  | GCGCCTTATC  | CGGTAACAT  | CGTCTTGAGT | CCAACCCGGT | AAGACACGAC | TTATCGCCAC |
|                                                           | GGGGCAAGTC | GGGCTGGCGA  | CGCGGAATAG  | GCCATTGATA | GCAGAACTCA | GGTGGGCCA  | TTCTGTGCTG | AATAGCGGTG |
| 2801                                                      | TGGCAGCAGC | CACTGGTAAC  | AGGATTAGCA  | GAGCGAGGTA | TGTAGGCGGT | GCTACAGAGT | TCTTGAAGTG | GTGGCCTAAC |
|                                                           | ACCGTCGTCG | GTGACCATTG  | TCCTAATCGT  | CTCGCTCCAT | ACATCCGCCA | CGATGTCTCA | AGAAGTTCAC | CACCGGATTG |
| 2881                                                      | TACGGCTACA | CTAGAAGGAC  | AGTATTTGGT  | ATCTGCGCTC | TGCTGAAGCC | AGTTACCTTC | GGAAAAAGAG | TTGGTAGCTC |
|                                                           | ATGCCGATGT | GATCTTCTG   | TCATAAACCA  | TAGACGCGAG | ACGACTTCGG | TCAATGGAAG | CCTTTTCTC  | AACCATCGAG |

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## FIGURE 7 - Page 3

2961 TTGATCCGGC AAACAAACCA CCGCTGGTAG CGGTGGTTTT TTTGTTTGCA AGCAGCAGAT TACGCGCAGA AAAAAAGGAT  
AACTAGGCCG TTTGTTTGGT GCGGACCATC GCCACCAAAA AAACAAACGT TCGTCGTCTA ATGCGCGTCT TTTTTCCTA

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3041 CTCRAGAAGA TCCTTTGATC TTTTCTACGG GGTCTGACGC TCAGTGGAAC GAAACTCAC GTTAAGGGAT TTTGGTCATG  
GAGTCTTCT AGGAACTAG AAAAGATGCC CCAGACTGCG AGTCACCTTG CTTTGGAGTG CAATCCCTA AAACAGTAG

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3121 AGATTATCAA AAAGGATCTT CACCTAGATC CTTTTAAAT AAAATGAAG TTTTAAATCA ATCTAAAGTA TATATGAGTA  
TCTAATAGT TTTCTAGAA GTGGATCTAG GAAAATTAA TTTTACTTC AAAATTTAGT TAGATTTCAT ATATACTCAT

---

3201 AACTTGGTCT GACAGTTACC AATGCTTAAT CAGTGAGGCA CCTATCTCAG CGATCTGTCT ATTTCGTTCA TCCATAGTTG  
TTGAACCAGA CTGTCAATGG TTACGAATTA GTCACCTCGT GGATAGAGTC GCTAGACAGA TAAAGCAAGT AGGTATCAAC

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3281 CCTGACTCCC CGTCGTGTAG ATAACTACGA TACGGGAGGG CTTACCATCT GGCCCCAGTG CTGCAATGAT ACCGCGAGAC  
GGACTGAGGG GCAGCACATC TATTGATGCT ATGCCCTCCC GAATGGTAGA CCGGGGTCAC GACGTTACTA TGGCGCTCTG

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3361 CCACGCTCAC CGGCTCCAGA TTTATCAGCA ATAAACCAGC CAGCCGGAAG GGCCGAGCGC AGAAGTGGTC CTGCAACTTT  
GGTGCGAGTG GCCGAGGTCT AAATAGTCGT TATTTGGTCG GTCGGCCTTC CCGGCTCGCG TCTTACCAG GACGTTGAAA

---

3441 ATCCGCTCC ATCCAGTCTA TTAATTGTTG CCGGGAAGCT AGAGTAAGTA GTTCGCCAGT TAATAGTTTG CGCAACGTTG  
TAGGCGGAGG TAGGTCAGAT AATTAACAAC GGCCCTTCGA TCTCATTCTA CAAGCGGTCA ATTATCAAAC GCGTTGCAAC

---

3521 TTGCCATTGC TACAGGCATC GTGGTGTAC GTCGTCGTT TGGTATGGCT TCATTAGCT CCGGTTCCCA ACGATCAAGG  
AACGGTAACG ATGTCCGTAG CACCACAGTG CGAGCAGCAA ACCATACCGA AGTAAGTCGA GGCCAAGGGT TGCTAGTTCC

---

3601 CGAGTTACAT GATCCCCAT GTTGTGCAAA AAAGCGGTTA GTCCTTCGG TCTCCGATC GTTGTGAGAA GTAAGTTGGC  
GCTCAATGTA CTAGGGGGTA CAACACGTTT TTTCCCAAT CGAGGAAGCC AGGAGGCTAG CAACAGTCTT CATTCAACCG

---

3681 CGCAGTGTTA TCACTCATGG TTATGGCAGC ACTGCATAAT TCTCTTACTG TCATGCCATC CGTAAGATGC TTTTCTGTGA  
GCGTCACAAT AGTGAGTACC AATACCGTCG TGACGTATTA AGAGAATGAC AGTACGGTAG GCATTCTACG AAAAGACACT

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3761 CTGGTGAGTA CTCAACCAAG TCATTCTGAG AATAGTGTAT CGGGCGACCG AGTTGCTCTT GCCCGGCGTC AATACGGGAT  
GACCACTCAT GAGTTGGTTC AGTAAGACTC TTATCACATA CGCCGCTGGC TCAACGAGAA CCGGCGCGAG TTATGCCCTA

---

3841 AATACCGCGC CACATAGCAG AACTTTAAAA GTGCTCATCA TTGGAACAG TTCTTCGGGG CGAAACTCT CAAGGATCTT  
TTATGGCGCG GTGTATCGTC TTGAAATTTT CACGAGTAGT AACCTTTTGC AAGAAGCCCC GCTTTTGAGA GTTCCTAGAA

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3921 ACCGCTGTTG AGATCCAGTT CGATGTAAC CACTCGTGCA CCCAAGTAT CTTGAGCATC TTTTACTTTC ACCAGCGTTT  
TGGCGACAAC TCTAGGTCAA GCTACATTGG GTGAGCACGT GGGTTGACTA GAAGTCGTAG AAAATGAAAG TGGTCGCAAA

---

4001 CTGGGTGAGC AAAACAGGA AGGCAAAATG CCGCAAAAAA GGAATAAAG GCGACACGGA AATGTTGAAT ACTCATACTC  
GACCCACTCG TTTTGTCTCT TCCGTTTAC GCGGTTTTT CCCTTATTCC CGCTGTGCCT TTACAACCTA TGAGTATGAG

---

4081 TTCCTTTTTT AATATTATTG AAGCATTAT CAGGGTTATT GTCTCATGAG CGGATACATA TTTGAATGTA TTTAGAAAAA  
AAGGAAAAG TTATAATAAC TTCGTAAATA GTCCCAATAA CAGAGTACT GCCTATGTAT AAACCTACAT AATCTTTTT

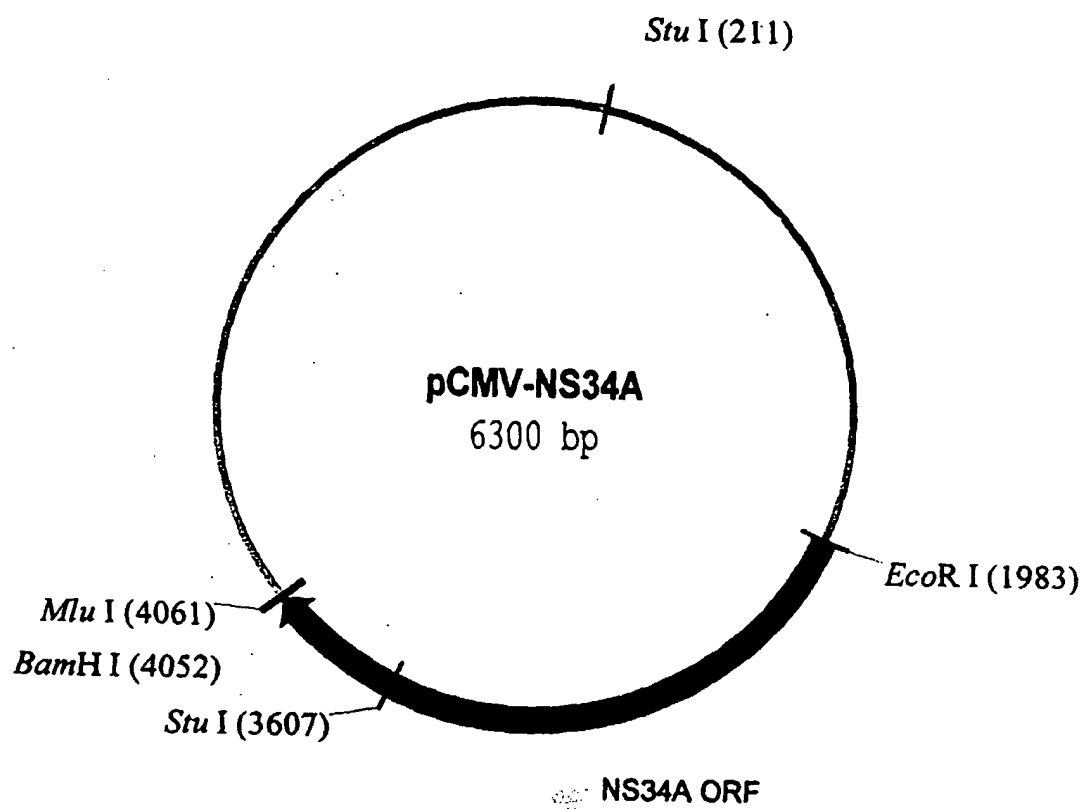
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4161 TAAACAAATA GGGGTTCCGC GCACATTTC CCGAAAAGTG CCACCTGACG TCTAAGAAAC CATTATTATC ATGACATTAA  
ATTTGTTTAT CCCAAGGCG CGTGTAAGG GGCTTTTAC GGTGGACTGC AGATTCTTG GTAATAATAG TACTGTAAT

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4241 CCTATAAAAA TAGGCGTATC ACGAGGCCCT TTCGTC  
GGATATTTTT ATCCGCATAG TGCTCCGGA AAGCAG

**FIGURE 8**



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## FIGURE 9 - Page 1

|       |            |            |            |            |            |
|-------|------------|------------|------------|------------|------------|
|       | TCGCGCGTTT | CGGTGATGAC | GGTGAAAACC | TCTGACACAT | GCAGCTCCCG |
|       | AGCGCGCAAA | GCCACTACTG | CCACTTTTGG | AGACTGTGTA | CGTCGAGGGC |
| <hr/> |            |            |            |            |            |
| 51    | GAGACGGTCA | CAGCTTGTCT | GTAAGCGGAT | GCCGGGAGCA | GACAAGCCCG |
|       | CTCTGCCAGT | GTCGAACAGA | CATTGCGCTA | CGGCCCTCGT | CTGTTGCGGC |
| <hr/> |            |            |            |            |            |
| 101   | TCAGGGCGCG | TCAGCGGGTG | TTGGCGGGTG | TCGGGGCTGG | CTTAACATG  |
|       | AGTCCCGCGC | AGTCGCCCAC | AACCGCCCAC | AGCCCCGACC | GAATTGATAC |
| <hr/> |            |            |            |            |            |
| 151   | CGGCATCAGA | GCAGATTGTA | CTGAGAGTGC | ACCATATGAA | GCTTTTGGCA |
|       | GCCGTAGTCT | CGTCTAACAT | GACTCTCACG | TGGTATACTT | CGAAAAACGT |
| <hr/> |            |            |            |            |            |
|       | StuI       |            |            |            |            |
|       | -----      |            |            |            |            |
| 201   | AAAGCCTAGG | CCTCCAAAAA | AGCCTCCTCA | CTACTTCTGG | AATAGCTCAG |
|       | TTTCGGATCC | GGAGGTTTTT | TCGGAGGAGT | GATGAAGACC | TTATCGAGTC |
| <hr/> |            |            |            |            |            |
| 251   | AGGCCGAGGC | GGCCTCGGCC | TCTGCATAAA | TAAAAAAAT  | TAGTCAGCCA |
|       | TCCGGCTCCG | CCGGAGCCCG | AGACGTATTT | ATTTTTTTTA | ATCAGTCGGT |
| <hr/> |            |            |            |            |            |
| 301   | TGGGGCGGAG | AATGGGCGGA | ACTGGGCGGG | GAGGGAATTA | TTGGCTATTG |
|       | ACCCCGCCTC | TTACCCGCCT | TGACCCGCCC | CTCCCTTAAT | AACCGATAAC |
| <hr/> |            |            |            |            |            |
| 351   | GCCATTGCAT | ACGTTGTATC | TATATCATAA | TATGTACATT | TATATTGGCT |
|       | CGGTAACGTA | TGCAACATAG | ATATAGTATT | ATACATGTAA | ATATAACCGA |
| <hr/> |            |            |            |            |            |
| 401   | CATGTCCAAT | ATGACCGCCA | TGTTGACATT | GATTATTGAC | TAGTTATTAA |
|       | GTACAGGTTA | TACTGGCGGT | ACAACTGTAA | CTAATAACTG | ATCAATAATT |
| <hr/> |            |            |            |            |            |
| 451   | TAGTAATCAA | TTACGGGGTC | ATTAGTTCAT | AGCCCATATA | TGGAGTTCCG |
|       | ATCATTAGTT | AATGCCCCAG | TAATCAAGTA | TCGGGTATAT | ACCTCAAGGC |
| <hr/> |            |            |            |            |            |
| 501   | CGTTACATAA | CTTACGGTAA | ATGGCCCCCC | TGGCTGACCG | CCCAACGACC |
|       | GCAATGTATT | GAATGCCATT | TACCGGGCGG | ACCGACTGGC | GGGTGTCTGG |
| <hr/> |            |            |            |            |            |
| 551   | CCCGCCCAT  | GACGTCAATA | ATGACGTATG | TCCCATAGT  | AACGCCAATA |
|       | GGCGGGGTAA | CTGCAGTTAT | TACTGCATAC | AAGGGTATCA | TTGCGGTTAT |
| <hr/> |            |            |            |            |            |
| 601   | GGGACTTTCC | ATTGACGTCA | ATGGGTGGAG | TATTTACGGT | AACTGCCCA  |
|       | CCCTGAAAGG | TAACTGCAGT | TACCCACCTC | ATAAATGCCA | TTTGACGGGT |
| <hr/> |            |            |            |            |            |
| 651   | CTTGGCAGTA | CATCAAGTGT | ATCATATGCC | AAGTCCGCCC | CCTATTGACG |
|       | GAACCGTCAT | GTAATTCACA | TAGTATACGG | TTCAGGCGGG | GGATAACTGC |
| <hr/> |            |            |            |            |            |
| 701   | TCAATGACGG | TAAATGGCCC | GCCTGGCATT | ATGCCAGTA  | CATGACCTTA |
|       | AGTTACTGCC | ATTTACCGGG | CGGACCGTAA | TACGGGTCAT | GTACTGGAAT |
| <hr/> |            |            |            |            |            |
| 751   | CGGGACTTTC | CTACTTGGCA | GTACATCTAC | GTATTAGTCA | TCGCTATTAC |
|       | GCCCTGAAAG | GATGAACCGT | CATGTAGATG | CATAATCAGT | AGCGATAATG |
| <hr/> |            |            |            |            |            |
| 801   | CATGGTGATG | CGGTTTTGGC | AGTACACCAA | TGGGCGTGGA | TAGCGGTTTG |
|       | GTACCACTAC | GCCAAAACCG | TCATGTGGTT | ACCCGCACCT | ATCGCCAAAC |
| <hr/> |            |            |            |            |            |
| 851   | ACTCACGGGG | ATTTCCAAGT | CTCCACCCCA | TTGACGTCAA | TGGGAGTTTG |
|       | TGAGTGCCCC | TAAAGGTTCA | GAGGTGGGGT | AACTGCAGTT | ACCCTCAAAC |

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**FIGURE 9 - Page 2**

|      |             |            |            |            |             |
|------|-------------|------------|------------|------------|-------------|
| 901  | TTTTGGCACC  | AAAATCAACG | GGACTTTCCA | AAATGTCGTA | ATAACCCCGC  |
|      | AAAACCGTGG  | TTTtagTTGC | CCTGAAAGGT | TTTACAGCAT | TATTGGGGCG  |
| 951  | CCCGTTGACG  | CAAATGGGCG | GtagGCGTGT | ACGGTGGGAG | GTCTATATAA  |
|      | GGGCAACTGC  | GTTTACCCGC | CATCCGCACA | TGCCACCCTC | CAGATATATT  |
| 1001 | GCAGAGCTCG  | TTTAGTGAAC | CGTCAGATCG | CCTGGAGACG | CCATCCACGC  |
|      | CGTCTCGAGC  | AAATCACTTG | GCAGTCTAGC | GGACCTCTGC | GGTAGGTGCG  |
| 1051 | TGTTTTGACC  | TCCATAGAAG | ACACCGGGAC | CGATCCAGCC | TCCGCGGCCG  |
|      | ACAAAACCTGG | AGGTATCTTC | TGTGGCCCTG | GCTAGGTCGG | AGGCGCCGGC  |
| 1101 | GGAACGGTGC  | ATTGGAACGC | GGATTCCCGG | TGCCAAGAGT | GACGTAAGTA  |
|      | CCTTGCCACG  | TAACCTTGCG | CCTAAGGGGC | ACGGTTCTCA | CTGCATTCTAT |
| 1151 | CCGCTATAG   | ACTCTATAGG | CACACCCCTT | TGGCTCTTAT | GCATGCTATA  |
|      | GGCGGATATC  | TGAGATATCC | GTGTGGGGAA | ACCGAGAATA | CGTACGATAT  |
| 1201 | CTGTTTTTGG  | CTTGGGGCCT | ATACACCCCC | GCTCCTTATG | CTATAGGTGA  |
|      | GACAAAAC    | GAACCCCGGA | TATGTGGGGG | CGAGGAATAC | GATATCCACT  |
| 1251 | TGGTATAGCT  | TAGCCTATAG | GTGTGGGTTA | TTGACCATTA | TTGACCACTC  |
|      | ACCATATCGA  | ATCGGATATC | CACACCCAAT | AACTGGTAAT | AACTGGTGAG  |
| 1301 | CCCTATTGGT  | GACGATACTT | TCCATTACTA | ATCCATAACA | TGGCTCTTTG  |
|      | GGGATAACCA  | CTGCTATGAA | AGGTAATGAT | TAGGTATTGT | ACCGAGAAAC  |
| 1351 | CCACAACATAT | CTCTATTGGC | TATATGCCAA | TACTCTGTCC | TTCAGAGACT  |
|      | GGTGTTGATA  | GAGATAACCG | ATATACGGTT | ATGAGACAGG | AAGTCTCTGA  |
| 1401 | GACACGGACT  | CTGTATTTTT | ACAGGATGGG | GTCCATTAT  | TATTTACAAA  |
|      | CTGTGCCTGA  | GACATAAAAA | TGTCTTACCC | CAGGTAAATA | ATAAATGTTT  |
| 1451 | TTACATATA   | CAACAACGCC | GTCCCCCGTG | CCCGCAGTTT | TTATTAAACA  |
|      | AAGTGATAT   | GTTGTTGCGG | CAGGGGGCAC | GGGCGTCAAA | AATAATTGT   |
| 1501 | TAGCGTGGA   | TCTCCGACAT | CTCGGGTACG | TGTTCCGGAC | ATGGGCTCTT  |
|      | ATCGCACCCCT | AGAGGCTGTA | GAGCCCATGC | ACAAGGCCTG | TACCCGAGAA  |
| 1551 | CTCCGGTAGC  | GGCGGAGCTT | CCACATCCGA | GCCCTGGTCC | CATCCGTCCA  |
|      | GAGGCCATCG  | CCGCCTCGAA | GGTGTAGGCT | CGGGACCAGG | GtagGCAGGT  |
| 1601 | GCGGCTCATG  | GTGCTCGGC  | AGCTCCTTGC | TCCTAACAGT | GGAGGCCAGA  |
|      | CGCCGAGTAC  | CAGCGAGCCG | TCGAGGAACG | AGGATTGTCA | CCTCCGGTCT  |
| 1651 | CTTAGGCACA  | GCACAATGCC | CACCACCACC | AGTGTGCCGC | ACAAGGCCGT  |
|      | GAATCCGTGT  | CGTGTTACGG | GTGGTGGTGG | TCACACGGCG | TGTTCCGGCA  |
| 1701 | GGCGGTAGGG  | TATGTGTCTG | AAAATGAGCT | CGGAGATTGG | GCTCGCACCT  |
|      | CCGCCATCCC  | ATACACAGAC | TTTACTCGA  | GCCTCTAACC | CGAGCGTGGA  |
| 1751 | GGACGCAGAT  | GGAAGACTTA | AGGCAGCGGC | AGAAGAAGAT | GCAGGCAGCT  |
|      | CCTGCGTCTA  | CCTTCTGAAT | TCCGTCGCCG | TCTTCTCTA  | CGTCCGTCGA  |
| 1801 | GAGTTGTTGT  | ATTCTGATAA | GAGTCAGAGG | TAACCTCCGT | TGCGGTGCTG  |
|      | CTCAACAACA  | TAAGACTATT | CTCAGTCTCC | ATTGAGGGCA | ACGCCACGAC  |

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## FIGURE 9 - Page 3

1851 TTAACGGTGG AGGGCAGTGT AGTCTGAGCA GTACTCGTTG CTGCCGCGCG  
AATTGCCACC TCCCGTCACA TCAGACTCGT CATGAGCAAC GACGGCGCGC

1901 CGCCACCAGA CATAATAGCT GACAGACTAA CAGACTGTTC CTTTCCATGG  
GCGGTGGTCT GTATTATCGA CTGTCTGATT GTCTGACAAG GAAAGGTACC

+2

M A P

EcoRI

1951 GTCTTTTCTG CAGTCACCGT CGTCGACCTA AGAATTCACC ATGGCGGCCA  
CAGAAAAGAC GTCAGTGGCA GCAGCTGGAT TCTTAAGTGG TACCGCGGGT

+2

2001 I T A Y A Q Q T R G L L G C I I T  
TCACGGCGTA CGCCAGCAG ACAAGGGGCC TCCTAGGGTG CATAATCACC  
AGTCCCGCAT GCGGTCGTC TGTCCCCGG AGGATCCAC GTATTAGTGG

+2

2051 S L T G R D K N Q V E G E V Q I V  
AGCCTAACTG GCCGGGACAA AAACCAAGTG GAGGGTGAGG TCCAGATTGT  
TCGGATTGAC CGGCCCTGTT TTTGGTTCAC CTCCCACTCC AGGTCTAACA

+2

2101 S T A A Q T F L A T C I N G V C  
GTCAACTGCT GCCCAACCT TCCTGGCAAC GTGCATCAAT GGGGTGTGCT  
CAGTTGACGA CGGGTTTGA AGGACCGTTG CACGTAGTTA CCCCACACGA

+2

2151 W T V Y H G A G T R T I A S P K G  
GGACTGTCTA CCACGGGGCC GGAACGAGGA CCATCGCGTC ACCCAAGGGT  
CCTGACAGAT GGTGCCCGG CTTTGCTCCT GGTAGCGCAG TGGGTTCCTA

+2

2201 P V I Q M Y T N V D Q D L V G W P  
CCTGTATCC AGATGTATAC CAATGTAGAC CAAGACCTTG TGGGCTGGCC  
GGACAGTAGG TCTACATATG GTTACATCTG GTTCTGGAAC ACCCGACCGG

+2

2251 A S Q G T R S L T P C T C G S S  
CGCTTCGCAA GGTACCGCT CATTGACACC CTGCACTTGC GGCTCCTCGG  
GCGAAGCGTT CCATGGGCGA GTAAGTGTG GACGTGAAC CCGAGGAGCC

+2

2301 D L Y L V T R H A D V I P V R R K  
ACCTTTACCT GGTACAGAGG CACGCCGATG TCATTCCCGT GCGCCGGCGG  
TGGAAATGGA CCAGTGCTCC GTGCGGCTAC AGTAAGGGCA CGCGCCCGCC

+2

2351 G D S R G S L L S P R P I S Y L K  
GGTGATAGCA GGGGCAGCCT GCTGTCGCCC CGGCCCATTT CTTACTTGAA  
CCACTATCGT CCCCCTCGGA CGACAGCGGG GCCGGGTAAG GGATGAACCT

+2

2401 G S S G G P L L C P A G H A V G  
AGGCTCCTCG GGGGGTCCGC TGTTGTGCCC CGCGGGGCAC GCCGTGGGCA  
TCCGAGGAGC CCCCAGGCG ACAACACGGG GCGCCCGTG CGGCACCCGT

+2

2451 I F R A A V C T R G V A K A V D F  
TATTTAGGGC CGCGGTGTGC ACCCGTGGAG TGGCTAAGGC GGTGGACTTT  
ATAAATCCCG GCGCCACACG TGGGCACCTC ACCGATTCCG CCACCTGAAA

+2

2501 I P V E N L E T T M R S P V F T D  
ATCCCTGTGG AGAACCTAGA GACAACCATG AGGTCCCCCG TGTTACGGA  
TAGGGACACC TCTTGATCT CTGTTGTAC TCCAGGGGCC ACAAGTGCCT

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## FIGURE 9 - Page 4

+2 N S S P P V V P Q S F Q V A H L  
 2551 TAACTCCTCT CCACCAGTAG TGCCCCAGAG CTTCCAGGTG GCTCACCTCC  
 ATTGAGGAGA GGTGGTCATC ACGGGGTCTC GAAGGTCCAC CGAGTGGAGG

---

+2 H A P T G S G K S T K V P A A Y A  
 2601 ATGCTCCAC AGGCAGCGGC AAAAGCACCA AGGTCCCGGC TGCAATATGCA  
 TACGAGGGTG TCCGTCGCCG TTTTCGTGGT TCCAGGGCCG ACGTATACGT

---

+2 A Q G Y K V L V L N P S V A A T L  
 2651 GCTCAGGGCT ATAAGGTGCT AGTACTCAAC CCCTCTGTTG CTGCAACACT  
 CGAGTCCCGA TATCCACGA TCATGAGTTG GGGAGACAAC GACGTTGTGA

---

+2 G F G A Y M S K A H G I D P N I  
 2701 GGGCTTTGGT GCTTACATGT CCAAGGCTCA TGGGATCGAT CCTAACATCA  
 CCCGAAACCA CGAATGTACA GGTCCGAGT ACCCTAGCTA GGATTGTAGT

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+2 R T G V R T I T T G S P I T Y S T  
 2751 GGACCGGGGT GAGAACAAAT ACCACTGGCA GCCCATCAC GTACTCCACC  
 CCTGCCCCCA CTCTGTGTTA TGGTGACCGT CGGGGTAGTG CATGAGGTGG

---

+2 Y G K F L A D G G C S G G A Y D I  
 2801 TACGGCAAGT TCCTTGCCGA CGGCGGGTGC TCGGGGGGCG CTTATGACAT  
 ATGCCGTTCA AGGAACGGCT GCCGCCACG AGCCCCCGC GAATACTGTA

---

+2 I I C D E C H S T D A T S I L G  
 2851 AATAATTTGT GACGAGTGCC ACTCCACGGA TGCCACATCC ATCTTGGGCA  
 TTATTAAACA CTGCTCACGG TGAGGTGCCT ACGGTGTAGG TAGAACCCGT

---

+2 I G T V L D Q A E T A G A R L V V  
 2901 TTGGCACTGT CCTTGACCAA GCAGAGACTG CGGGGGCGAG ACTGGTTGTG  
 AACCGTGACA GGAAGTGGT CGTCTGTGAC GCCCCCGCTC TGACCAACAC

---

+2 L A T A T P P G S V T V P H P N I  
 2951 CTCGCCACCG CCACCCCTCC GGGCTCCGTC ACTGTGCCCC ATCCCAACAT  
 GAGCGGTGGC GGTGGGGAGG CCGGAGGAG TGACACGGGG TAGGGTTGTA

---

+2 E E V A L S T T G E I P F Y G K  
 3001 CGAGGAGGTT GCTCTGTCCA CCACCGGAGA GATCCCTTTT TACGGCAAGG  
 GCTCCTCCAA CGAGACAGGT GGTGGCCTCT CTAGGGAAAA ATGCCGTTC

---

+2 A I P L E V I K G G R H L I F C H  
 3051 CTATCCCCCT CGAAGTAATC AAGGGGGGGA GACATCTCAT CTTCTGTCAT  
 GATAGGGGGA GCTTCATTAG TTCCCCCCT CTGTAGAGTA GAAGACAGTA

---

+2 S K K K C D E L A A K L V A L G I  
 3101 TCAAAGAAGA AGTGCGACGA ACTCGCCGCA AAGCTGGTCG CATTGGGCAT  
 AGTTTCTTCT TCACGCTGCT TGAGCGGCGT TTCGACCAGC GTAACCCGTA

---

+2 N A V A Y Y R G L D V S V I P T  
 3151 CAATGCCGTG GCTTACTACC GCGGTCTTGA CGTGTCCGTC ATCCCGACCA  
 GTTACGGCAC CGGATGATGG CGCCAGAACT GCACAGGCAG TAGGGCTGGT

---

+2 S G D V V V V A T D A L M T G Y T  
 3201 CGGGCGATGT TGTCGTCGTG GCAACCGATG CCCTCATGAC CGGCTATACC  
 CGCCGCTACA ACAGCAGCAC CGTTGGCTAC GGGAGTACTG GCCGATATGG

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## FIGURE 9 - Page 5

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+2 G D F D S V I D C N T C V T Q T V
3251 GGC GACTTCG ACTCGGTGAT AGACTGCAAT ACGTGTGTCA CCCAGACAGT
    CCGTGAAGC TGAGCCACTA TCTGACGTTA TGCACACAGT GGGTCTGTCA

+2 D F S L D P T F T I E T I T L P
3301 CGATTTCAGC CTTGACCCTA CCTTCACCAT TGAGACAATC ACGTCCCCC
    GCTAAAGTCG GAACTGGGAT GGAAGTGGTA ACTCTGTTAG TGCGAGGGGG

+2 Q D A V S R T Q R R G R T G R G K
3351 AAGATGCTGT CTCCCGCACT CAACGTCGGG GCAGGACTGG CAGGGGGAAG
    TTCTACGACA GAGGGCGTGA GTTGACAGCC CGTCCTGACC GTCCCCCTTC

+2 P G I Y R F V A P G E R P S G M F
3401 CCAGGCATCT ACAGATTGTG GGCACCGGGG GAGCGCCCTT CCGGCATGTT
    GGTCCGTAGA TGTCTAAACA CCGTGCCCCC CTCGCGGGGA GGCCGTACAA

+2 D S S V L C E C Y D A G C A W Y
3451 CGACTCGTCC GTCCTCTGTG AGTGCTATGA CGCAGGCTGT GCTTGGTATG
    GCTGAGCAGG CAGGAGACAC TCACGATACT GCGTCCGACA CGAACCATAC

+2 E L T P A E T T V R L R A Y M N T
3501 AGCTCACGCC CGCGAGACT ACAGTTAGGC TACGAGCGTA CATGAACACC
    TCGAGTGCGG GCGGCTCTGA TGTCAATCCG ATGCTCGCAT GTACTTGTGG

+2 P G L P V C Q D H L E F W E G V F
3551 CCGGGGCTTC CCGTGTGCCA GGACCATCTT GAATTTTGGG AGGGCGTCTT
    GGCCCCGAAG GGCACACGGT CCTGGTAGAA CTAAAAACC TCCCGCAGAA

+2 T G L T H I D A H F L S Q T K Q
    Stul
    -----
3601 TACAGGCCTC ACTCATATAG ATGCCCACTT TCTATCCCAG ACAAAGCAGA
    ATGTCCGGAG TGAGTATATC TACGGGTGAA AGATAGGGTC TGTTTCGTCT

+2 S G E N L P Y L V A Y Q A T V C A
3651 TTGGGGAGAA CCTTCCTTAC CTGGTAGCGT ACCAAGCCAC CGTGTGCGCT
    CACCCCTCTT GGAAGGAATG GACCATCGCA TGGTTCGGTG GCACACGCGA

+2 R A Q A P P P S W D Q M W K C L I
3701 AGGGCTCAAG CCCCTCCCCC ATCGTGGGAC CAGATGTGGA AGTGTTTGAT
    TCCCGAGTTC GGGGAGGGGG TAGCACCTGT GTCTACACCT TCACAACTA

+2 R L K P T L H G P T P L L Y R L
3751 TCGCTCAAG CCCACCTCC ATGGGCCAAC ACCCTGCTA TACAGACTGG
    AGCGGAGTTC GGGTGGGAGG TACCCGGTTG TGGGACGAT ATGTCTGACC

+2 G A V Q N E I T L T H P V T K Y I
3801 GCGCTGTCA GAATGAAATC ACCCTGACGC ACCCAGTCAC CAAATACATC
    CGCGACAAGT CTTACTTTAG TGGGACTGCG TGGGTCAGTG GTTTATGTAG

+2 M T C M S A D L E V V T S T W V L
3851 ATGACATGCA TGTCGGCCGA CCTGGAGGTC GTCACGAGCA CCTGGGTGCT
    TACTGTACGT ACAGCCGGCT GGACCTCCAG CAGTGCTCGT GGACCCACGA

+2 V G G V L A A L A A Y C L S T G
3901 CGTTGGCGGC GTCCTGGCTG CTTTGGCCGC GTATTGCCTG TCAACAGGCT
    GCAACCGCGG CAGGACCGAC GAAACCGCG CATAACGGAC AGTTGTCCGA

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## FIGURE 9 - Page 6

+2 C V V I V G R V V L S G K P A I I  
 3951 GCGTGGTCAT AGTGGGCAGG GTCGTCTTGT CCGGGAAGCC GGCAATCATA  
 CGCACCAGTA TCACCCGTCC CAGCAGAACA GGCCCTTCGG CCGTTAGTAT

+2 P D R E V L Y R E F D E M E E C  
 4001 CCTGACAGGG AAGTCCTCTA CCGAGAGTTC GATGAGATGG AAGAGTGCTA  
 GGACTGTCCC TTCAGGAGAT GGCTCTCAAG CTACTCTACC TTCTCACGAT

BamHI MluI  
 -----  
 4051 GGATCCACTA CGCGTTAGAG CTCGCTGATC AGCCTCGACT GTGCCTTCTA  
 CCTAGGTGAT GCGCAATCTC GAGCGACTAG TCGGAGCTGA CACGGAAGAT

4101 GTTGCCAGCC ATCTGTTGTT TGCCCTCTCC CCGTGCCTTC CTTGACCCTG  
 CAACGGTCGG TAGACAACAA ACGGGGAGGG GGCACGGAAG GAACTGGGAC

4151 GAAGGTGCCA CTCCCACTGT CCTTTCCTAA TAAAATGAGG AAATTGCATC  
 CTTCCACGGT GAGGGTGACA GGAAAGGATT ATTTTACTCC TTAAACGTAG

4201 GCATTGTCTG AGTAGGTGTC ATTCTATTCT GGGGGGTGGG GTGGGGCAGG  
 CGTAACAGAC TCATCCACAG TAAGATAAGA CCCCCACCC CACCCCGTCC

4251 ACAGCAAGGG GGAGGATTGG GAAGACAATA GCAGGCATGC TGGGGAGCTC  
 TGTGCTTCCC CCTCCTAACC CTTCTGTTAT CGTCCGTACG ACCCCTCGAG

4301 TTCCGCTTCC TCGCTCACTG ACTCGCTGCG CTCGGTCTGT CCGCTGCGGC  
 AAGGCGAAGG AGCGAGTGAC TGAGCGACGC GAGCCAGCAA GCCGACGCCG

4351 GAGCGGTATC AGCTCACTCA AAGCGGTAA TACGGTTATC CACAGAATCA  
 CTCGCCATAG TCGAGTGAGT TTCCGCCATT ATGCCAATAG GTGTCTTAGT

4401 GGGGATAACG CAGGAAAGAA CATGTGAGCA AAAGGCCAGC AAAAGGCCAG  
 CCCCTATTGC GTCCTTTCTT GTACACTCGT TTTCCGGTCG TTTTCCGGTC

4451 GAACCGTAAA AAGGCCGCGT TGCTGGCGTT TTTCCATAGG CTCCGCCCCC  
 CTTGGCATT TTCCGGCGCA ACGACCGCAA AAAGGTATCC GAGGCGGGGG

4501 CTGACGAGCA TCACAAAAAT CGACGCTCAA GTCAGAGGTG GCGAAACCCG  
 GACTGCTCGT AGTGTTTTTA GCTGCGAGTT CAGTCTCCAC CGCTTTGGGC

4551 ACAGGACTAT AAAGATACCA GCGGTTTCCC CCTGGAAGCT CCCTCGTGCG  
 TGTCTGATA TTTCTATGGT CCGCAAAGGG GGACCTTCGA GGGAGCACGC

4601 CTCTCCTGTT CCGACCTGCG CGCTTACCGG ATACCTGTCC GCCTTTCTCC  
 GAGAGGACAA GGCTGGGACG GCGAATGGCC TATGGACAGG CGGAAAGAGG

4651 CTTCCGGGAAG CGTGGCGCTT TCTCAATGCT CACGCTGTAG GTATCTCAGT  
 GAAGCCCTTC GCACCGCGAA AGAGTTACGA GTGCGACATC CATAGAGTCA

4701 TCGGTGTAGG TCGTTGCTC CAAGCTGGGC TGTGTGCAGG AACCCCGGT  
 AGCCACATCC AGCAAGCGAG GTTCGACCG ACACACGTG TTGGGGGGCA

4751 TCAGCCCGAC CGTGCGCCT TATCCGGTAA CTATCGTCTT GAGTCCAACC  
 AGTCGGGCTG GCGACGCGGA ATAGGCCATT GATAGCAGAA CTCAGGTTGG

4801 CGGTAAGACA CGACTTATCG CCACTGGCAG CAGCCACTGG TAACAGGATT  
 GCCATTCTGT GCTGAATAGC GGTGACCGTC GTCGGTGACC ATTGTCCTAA

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**FIGURE 9 - Page 7**

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4851 AGCAGAGCGA GGTATGTAGG CGGTGCTACA GAGTTCTTGA AGTGGTGGCC
TCGTCTCGCT CCATACATCC GCCACGATGT CTCAAGAACT TCACCACCGG

4901 TAACTACGGC TACTACTAGAA GGACAGTATT TGGTATCTGC GCTCTGCTGA
ATTGATGCCG ATGTGATCTT CCTGTCATAA ACCATAGACG CGAGACGACT

4951 AGCCAGTTAC CTTCCGAAAA AGAGTTGGTA GCTCTTGATC CGGCAAACAA
TCGGTCAATG GAAGCCTTTT TCTCAACCAT CGAGAAGTAG GCCGTTTGTT

5001 ACCACCGCTG GTAGCGGTGG TTTTTTTGTT TGCAAGCAGC AGATTACGCG
TGGTGGCGAC CATCGCCACC AAAAAACAA ACGTTCGTCG TCTAATGCGC

5051 CAGAAAAAAA GGATCTCAAG AAGATCCTTT GATCTTTTCT ACGGGGTCTG
GTCTTTTTTT CCTAGAGTTC TTCTAGGAAA CTAGAAAAGA TGCCCCAGAC

5101 ACGCTCAGTG GAACGAAAAC TCACGTTAAG GGATTTTGGT CATGAGATTA
TGCGAGTCAC CTGCTTTTG AGTGCAATTC CCTAAACCA GTACTCTAAT

5151 TCAAAAAGGA TCTTCACCTA GATCCTTTTA AATTAAAAAT GAAGTTTAA
AGTTTTTCCT AGAAGTGGAT CTAGGAAAAT TTAATTTTAA CTTCAAAAT

5201 ATCAATCTAA AGTATATATG AGTAACTTG GTCTGACAGT TACCAATGCT
TAGTTAGATT TCATATATAC TCATTTGAAC CAGACTGTCA ATGGTTACGA

5251 TAATCAGTGA GGCACCTATC TCAGCGATCT GTCTATTTTG TTCATCCATA
ATTAGTCACT CCGTGGATAG AGTCGCTAGA CAGATAAAGC AAGTAGGTAT

5301 GTTGCCTGAC TCCCCGTCGT GTAGATAACT ACGATACGGG AGGGCTTACC
CAACGGACTG AGGGGAGCA CATCTATTGA TGCTATGCCC TCCCGAATGG

5351 ATCTGGCCCC AGTGCTGCAA TGATACCGCG AGACCCACGC TCACCGGCTC
TAGACCGGGG TCACGACGTT ACTATGGCGC TCTGGGTGCG AGTGCCGAG

5401 CAGATTTATC AGCAATAAAC CAGCCAGCCG GAAGGGCCGA GCGCAGAAAT
GTCTAAATAG TCGTTATTTG GTCGGTCGGC CTTCCCGGCT CGCGTCTTCA

5451 GGTCTGCAA CTTTATCCGC CTCCATCCAG TCTATTAATT GTTGCCGGGA
CCAGGACGTT GAAATAGGCG GAGGTAGGTC AGATAATTAA CAACGGCCCT

5501 AGCTAGAGTA AGTAGTTCGC CAGTTAATAG TTTGCGCAAC GTTGTGCCA
TCGATCTCAT TCATCAAGCG GTCAATTATC AAACGCGTTG CAACAACGGT

5551 TTGCTACAGG CATCGTGGTG TCACGCTCGT CGTTTGGTAT GGCTTCATTC
AACGATGTCC GTAGACCAC AGTGCGAGCA GCAAACCATA CCGAAGTAAG

5601 AGCTCCGGTT CCAACGATC AAGGCGAGTT ACATGATCCC CCATGTTGTG
TCGAGGCCAA GGGTTGCTAG TTCCGCTCAA TGTACTAGGG GGTACAACAC

5651 CAAAAAGCG GTTAGCTCCT TCGGTCCTCC GATCGTTGTC AGAAGTAAGT
GTTTTTCGC CAATCGAGGA AGCCAGGAGG CTAGCAACAG TCTTCATTCA

5701 TGGCCGAGT GTTATCACTC ATGGTTATGG CAGCACTGCA TAATTCTCTT
ACCGGCGTCA CAATAGTGAG TACCAATACC GTCGTGACGT ATTAAGAGAA

5751 ACTGTCATGC CATCCGTAAG ATGCTTTTCT GTGACTGGTG AGTACTCAAC
TGACAGTACG GTAGGCATTC TACGAAAAGA CACTGACCAC TCATGAGTTG

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## FIGURE 9 - Page 8

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5801 CAAGTCATTG TGAGAATAGT GTATGCGGCG ACCGAGTTGC TCTTGCCCGG
      GTTCAGTAAG ACTCTTATCA CATACGCCGC TGGCTCAACG AGAACGGGCC

5851 CGTCAATACG GGATAATACC GCGCCACATA GCAGAACTTT AAAAGTGCTC
      GCAGTTATGC CCTATTATGG CGCGGTGTAT CGTCTTGAAA TTTTCACGAG

5901 ATCATTGGAA AACGTTCTTC GGGGCGAAAA CTCTCAAGGA TCTTACCGCT
      TAGTAACCTT TTGCAAGAAG CCCCGCTTTT GAGAGTTCCT AGAATGGCGA

5951 GTTGAGATCC AGTTCGATGT AACCCTACTCG TGCACCCAAC TGATCTTCAG
      CAACTCTAGG TCAAGCTACA TTGGGTGAGC ACGTGGGTG ACTAGAAGTC

6001 CATCTTTTAC TTTCAACAGC GTTCTGGGT GAGCAAAAAC AGGAAGGCAA
      GTAGAAAATG AAAGTGGTCG CAAAGACCCA CTCGTTTTTG TCCTTCCGTT

6051 AATGCCGCAA AAAAGGGAAT AAGGGCGACA CGGAAATGTT GAATACTCAT
      TTACGGCGTT TTTCCCTTA TTCCCGCTGT GCCTTTACAA CTTATGAGTA

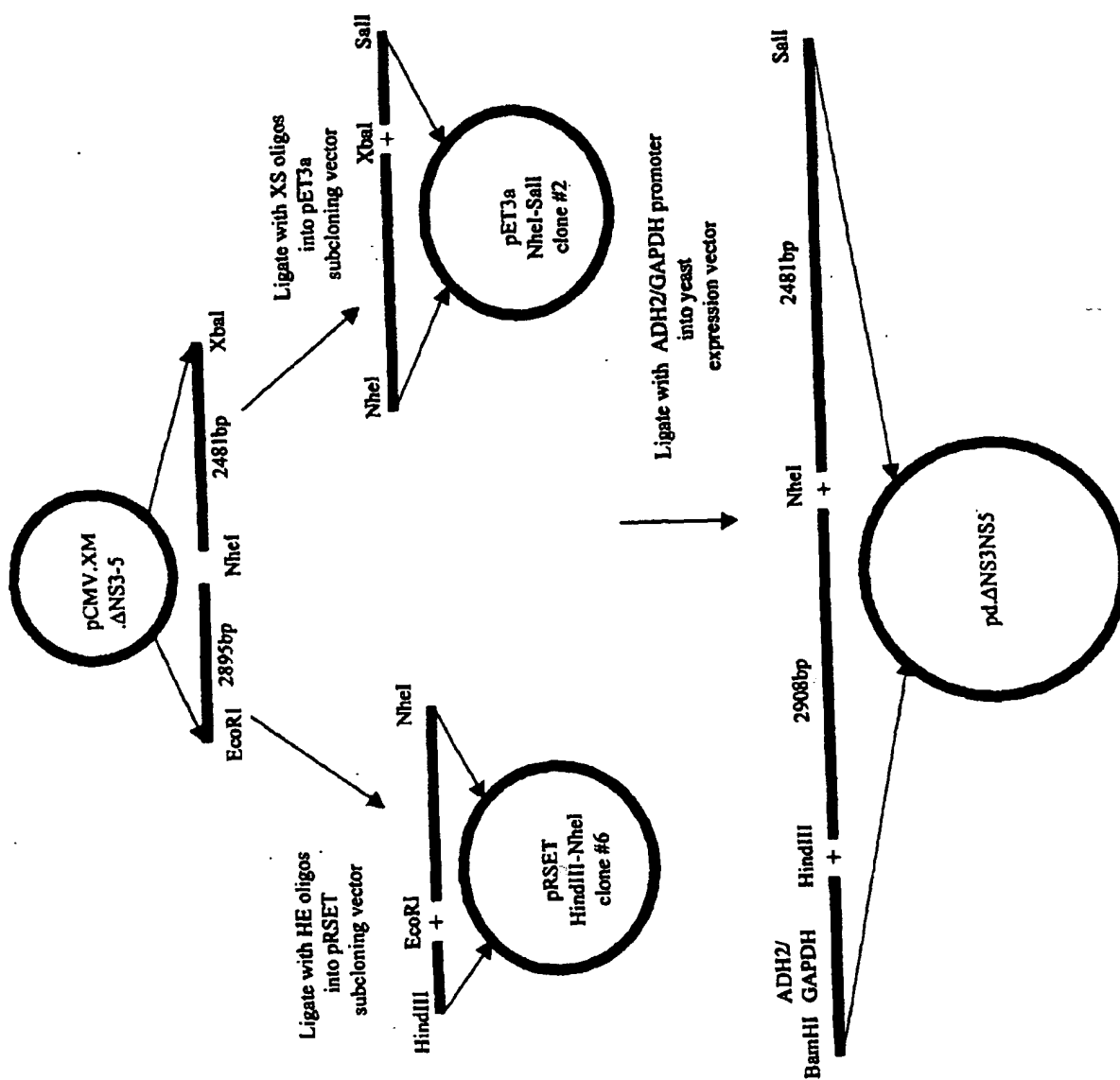
6101 ACTCTTCCTT TTTCAATATT ATTGAAGCAT TTATCAGGGT TATTGTCTCA
      TGAGAAGGAA AAAGTTATAA TAACTTCGTA AATAGTCCCA ATAACAGAGT

6151 TGAGCGGATA CATATTTGAA TGTATTTAGA AAAATAAACA AATAGGGGTT
      ACTCGCCTAT GTATAAACTT ACATAAATCT TTTTATTGT TTATCCCCAA

6201 CCGCGCACAT TTCCCCGAAA AGTGCCACCT GACGTCTAAG AAACCATTAT
      GGCGCGTGTA AAGGGGCTTT TCACGGTGGA CTGCAGATTC TTTGGTAATA

6251 TATCATGACA TTAACCTATA AAAATAGGCG TATCACGAGG CCCTTTCGTC
      ATAGTACTGT AATTGGATAT TTTTATCCGC ATAGTGCTCC GGGAAAGCAG
```

FIGURE 10



## FIGURE 11 - Page 1

M tAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuVal  
 2 AGCTTACAAAACAAATTCACCATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTA  
 TCGAATGTTTTGTTTAAGTGGTACCGACGTATACGTCGAGTCCCGATATTCCACGATCAT  
 ^ ^ ^ ^  
 1 HIND3, 21 NCOI, 30 NDEI, 58 SCAI,  
  
 LeuAsnProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGly  
 62 CTCAACCCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGG  
 GAGTTGGGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCC  
  
 IleAspProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyr  
 122 ATCGATCCTAACATCAGGACCGGGGTGAGAACAATTACCACTGGCAGCCCCATCAGTAC  
 TAGCTAGGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGCATG  
 ^  
 122 CLAI,  
  
 SerThrTyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIle  
 182 TCCACCTACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATA  
 AGGTGGATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGGAATACTGTATTAT  
  
 IleCysAspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeu  
 242 ATTTGTGACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTT  
 TAAACACTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAA  
  
 AspGlnAlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGly  
 302 GACCAAGCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGC  
 CTGGTTCTCTCTGACGCCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCCG  
 ^  
 309 ALWN1,  
  
 SerValThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIle  
 362 TCCGTCAGTGTGCCCCATCCCAACATCGAGGAGGTTGCTCTGTCCACCACCGGAGAGATC  
 AGGCAGTGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAG  
  
 ProPheTyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePhe  
 422 CCTTTTACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGGAGACATCTCATCTTC  
 GGAAAAATGCCGTTCCGATAGGGGGAGCTTCATTAGTCCCCCCCCTCTGTAGAGTAGAAG  
  
 CysHisSerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsn  
 482 TGTCAATTCAAAGAAGAGTGCGACGAACTCGCGCGAAAGCTGGTCGCATTGGGCATCAAT  
 ACAGTAAGTTTCTTCTTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTA  
  
 AlaValAlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValVal  
 542 GCCGTGGCCTACTACCGCGGTCTTGACGTGTCCGTATCCCGACCAGCGGCGATGTTGTC  
 CGGCACCGGATGATGGCGCCAGAAGTGCACAGGCAGTAGGGCTGGTCGCCGCTACAACAG  
 ^ ^  
 556 SAC2, 566 DRD1,  
  
 ValValAlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAsp  
 602 GTCGTGGCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGAC  
 CAGCACCGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTG  
 ^  
 621 BSPH1,  
  
 CysAsnThrCysValThrGlnThrValAspPheSerL uAspProThrPheThrIleGlu

## FIGURE 11 - Page 2

662 TGCAATACGTGTGTCACCCAGACAGTCGATTTTCAGCCTTGACCCTACCTTCACCATTGAG  
 ACGTTATGCACACAGTGGGTCTGTACAGTAAAGTCGGAAC TGGGATGGAAGTGGTAAC T  
  
 ThrIleThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArg  
 722 ACAATCACGCTCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGG  
 TGT TAGTGCGAGGGGGTTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCCTGACCGTCC  
  
 GlyLysProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAsp  
 782 GGAAGCCAGGCATCTACAGATTTGTGGCACCGGGGAGCGCCCTCCGGCATGTTTCGAC  
 CCCTTCGGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTG  
  
 822 BGLI, 839 DRD1,  
  
 SerSerValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAla  
 842 TCGTCCGTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCGCC  
 AGCAGGCAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAGTGCGGGCGG  
  
 887 SACI,  
  
 GluThrThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAsp  
 902 GAGACTACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGAC  
 CTCTGATGTCAATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCTCTG  
  
 937 SMAI XMAI,  
  
 HisLeuGluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeu  
 962 CATCTTGAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCCACTTTCTA  
 GTAGAACTTAAAACCTCCCGCAGAAATGTCGGGAGTGAGTATATCTACGGGTGAAAGAT  
  
 991 STUI,  
  
 SerGlnThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrVal  
 1022 TCCAGACAAAGCAGAGTGGGGAGAACCTTCCTTACCTGGTAGCGTACCAAGCCACCGTG  
 AGGGTCTGTTTCGTCTCACCCCTCTTGAAGGAATGGACCATCGCATGGTTCGGTGGCAC  
  
 1075 DRA3,  
  
 CysAlaArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArg  
 1082 TGGCTAGGGCTCAAGCCCTCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTTCGC  
 ACGCATCCCGAGTTCGGGGAGGGGGTAGCACCTGGTCTACACCTTCACAACTAAGCG  
  
 LeuLysProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsn  
 1142 CTCAAGCCCACCTCCATGGGCCAACCCCTGCTATACAGACTGGGCGCTGTTTCAAGAT  
 GAGTTCGGGTGGGAGGTACCCGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTA  
  
 1156 NCOI,  
  
 GluIleThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeu  
 1202 GAAATCACCTGACGCACCCAGTCACCAAATACATCATGACATGCATGTCGGCCGACCTG  
 CTTTAGTGGGACTGCGTGGGTGAGTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGAC  
  
 1236 BSPH1, 1240 DRD1, 1243 AVA3, 1251 EAG1 XMA3, 1256 DRD1,  
  
 GluValValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyr  
 1262 GAGGTCGTCACGAGCACCTGGGTGCTCGTTGGCGGCGTCTGGCTGCTTTGGCCGCGTAT  
 CTCCAGCAGTGCTCGTGGACCCACGAGCAACCGCCGAGGACCGACGAAACCGGCGCATA

## FIGURE 11 - Page 3

CysLeuS rThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAla  
 1322 TGCCTGTCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCGTCTTGTCGGGAAGCCGGCA  
 ACGGACAGTTGTCCGACGCACCAAGTATCACCCGTCCCAGCAGAACAGGCCCTTCGGCCGT  
 1375 NAEI,  
 IleIleProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGln  
 1382 ATCATACCTGACAGGGAAGTCCTCTACCGAGAGTTCGATGAGATGGAAGAGTGCTCTCAG  
 TAGTATGGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCACGAGAGTC  
 1391 DRD1,  
 HisLeuProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeu  
 1442 CACTTACCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAGAAGGCCCTC  
 GTGAATGGCATGTAGCTCGTTCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCGGGGAG  
 GlyLeuLeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsn  
 1502 GGCCTCCTGCAGACCGCTCCCGTCAGGCAGAGGTTATCGCCCCTGCTGTCCAGACCAAC  
 CCGGAGGACGTCTGGCGCAGGGCAGTCCGTCTCCAATAGCGGGGACGACAGGTCTGGTTG  
 1508 PSTI, 1513 TTH3I,  
 TrpGlnLysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGln  
 1562 TGGCAAAACTCGAGACCTTCTGGGCGAAGCATATGTGGAAGTTCATCAGTGGGATACAA  
 ACCGTTTTTGAGCTCTGGAAGACCCGCTTCGTATACACCTGAAGTAGTCACCCATGTT  
 1571 XHOI, 1592 NDEI,  
 TyrLeuAlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPhe  
 1622 TACTTGGCGGGCTTGTCACGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTT  
 ATGAACCGCCCAACAGTTGCGACGGACCATGGGGCGGTAACGAAGTAACACCGAAAA  
 1649 BSTE2,  
 ThrAlaAlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGly  
 1682 ACAGCTGCTGTACACGCCCCACTAACCCTAGCCAAACCCTCTTCAACATATTGGGG  
 TGTCGACGACAGTGGTTCGGGTGATTGGTGATCGGTTGGGAGGAGAAGTTGTATAACCCC  
 1683 ALWN1 PVU2,  
 GlyTrpValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGly  
 1742 GGGTGGGTGGCTGCCCAGCTCGCCGCCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGC  
 CCCACCCACCGACGGGTGAGCGCGGGGGCCACGGCGATGACGGAACACCCGCGACCG  
 1800 ESP1,  
 LeuAlaGlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAla  
 1802 TTAGCTGGCGCCGCCATCGGCAGTGTGGACTGGGGAAGGTCCTCATAGACATCCTTGCA  
 AATCGACCGCGCGGTAGCCGTCAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGT  
 1808 KAS1 NARI,  
 GlyTyrGlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluVal  
 1862 GGGTATGGCGGGCGGTGGCGGGAGCTCTTGTCGTCATTCAAGATCATGAGCGGTGAGGTC  
 CCCATACCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAG

## FIGURE 11 - Page 4

1884 SACI, 1905 BSPH1,  
ProSerThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuVal  
1922 CCCTCCACGGAGGACCTGGTCAATCTACTGCCCCGCCATCCTCTCGCCCGGAGCCCTCGTA  
GGGAGGTGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCAT  
1934 TTH3I,  
ValGlyValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaVal  
1982 GTCGGCGTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCGGGCAGGGGGCAGTG  
CAGCCGCACCAGACACGTCGTTATGACGCGGCCGTGCAACCGGGCCCGCTCCCCCGTCAC  
2010 NAEI, 2023 SMAI XMAI,  
GlnTrpMetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHis  
2042 CAGTGGATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTTCCCCACGCAC  
GTCACCTACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGGTGCGTG  
2073 SMAI XMAI, 2099 DRA3,  
TyrValProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrVal  
2102 TACGTGCCGGAGAGCGATGCAGCTGCCCGCGTCACTGCCATACTCAGCAGCCTCACTGTA  
ATGCACGGCCTCTCGCTACGTGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACAT  
2121 PVU2,  
ThrGlnLeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSer  
2162 ACCCAGCTCCTGAGGCGACTGCACCACTGGATAAGCTCGGAGTGTAACCACTCCATGCTCC  
TGGGTCGAGGACTCCGCTGACGTGGTCACCTATTTCGAGCCTCACATGGTGAGGTACGAGG  
2165 ALWN1, 2170 MST2,  
GlySerTrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThr  
2222 GGTTCCTGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACC  
CCAAGGACCGATTCCCTGTAGACCCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGG  
2226 ECON1,  
TrpLeuLysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArg  
2282 TGGCTAAAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCTTTGTGTCCTGCCAGCGC  
ACCGATTTTCGATTTCGAGTACGGTGTGCGACGGACCCTAGGGGAAACACAGGACGGTCGGG  
2291 ESP1, 2306 PVU2, 2316 BAMHI,  
GlyTyrLysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAla  
2342 GGGTATAAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCT  
CCCATATTCGCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGA  
GluIleThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArg  
2402 GAGATCACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCCTAGGACCTGCAGG  
CTCTAGTGACCTGTACAGTTTTCGCCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCC  
2431 BSAB1, 2447 AVR2, 2454 SSE83871, 2455 PSTI,  
AsnMetTrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeu  
2462 AACATGTGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCCCTGTACCCCCCTT  
TTGTACACCTCACCTGGAAGGGGTAATTACGGATGTGGTGCCCGGGGACATGGGGGGAA



## FIGURE 11 - Page 5

2486 ASE1, 2503 APAI,  
ProAlaProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIle  
2522 CCTGCGCCGAACACTACACGTTTCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATA  
GGACGCGGCTTGATGTGCAAGCGCGATACCTCCACAGACGTCTCCTTATGCACCTCTAT  
2559 PSTI,  
ArgGlnValGlyAspPheHisTyrValThrGlyMetThrThrAspAsnLeuLysCysPro  
2582 AGGCAGGTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCCG  
TCCGTCCACCCCTGAAGGTGATGCACTGCCCATCTGATGACTGTTAGAATTTACGGGC  
2600 DRA3,  
CysGlnValProSerProGluPhePheThrGluLeuAspGlyValArgLeuHisArgPhe  
2642 TGCCAGGTCCCATCGCCGAATTTTTCACAGAATTGGACGGGGTGCCTACATAGGTTT  
ACGGTCCAGGGTAGCGGGCTTAAAAAGTGTCTTAACCTGCCCCACGCGGATGTATCCAA  
2702 AlaProProCysLysProLeuLeuArgGluGluValSerPheArgValGlyLeuHisGlu  
GCGCCCCCTGCAAGCCCTTGCTGCGGGAGGAGGTATCATTGAGAGTAGGACTCCACGAA  
CGCGGGGGACGTTTCGGGAACGACGCCCTCCTCCATAGTAAGTCTCATCTGAGGTGCTT  
2762 TyrProValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSer  
TACCCGGTAGGGTCGCAATTACCTTGCAGCCCCGAACCGGACGTGGCCGTGTTGACGTCC  
ATGGGCCATCCCAGCGTTAATGGAACGCTCGGGCTTGGCTGCACCGGCACAACTGCAGG  
2763 HGIE2, 2815 AAT2,  
MetLeuThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGly  
2822 ATGCTCACTGATCCCTCCCATATAACAGCAGAGGCGGCCGGCGGAAGGTTGGCAGGGGA  
TACGAGTGACTAGGGAGGGTATATTGTCTCTCCGCCGGCCGCTTCCAACCGCTCCCT  
2856 EAG1 XMA3,  
SerProProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAla  
2882 TCACCCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCA  
AGTGGGGGAGACACCGGTCGAGGAGCCGATCGGTCGATAGGCGAGGTAGAGAGTTCCGT  
2895 BALI, 2909 NHEI,  
ThrCysThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuLeuTrp  
2942 ACTTGCACCGCTAACCATGACTCCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGG  
TGAACGTGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGGTTGGAGGATACC  
2972 ESP1, 2975 SACI,  
ArgGlnGluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeu  
3002 AGGCAGGAGATGGGCGGCAACATCACCAGGGTTGAGTCAGAAAACAAAGTGGTGATTCTG  
TCCGTCTCTACCCGCCGTTGTAGTGGTCCCACTCAGTCTTTGTTTACCCTAAGAC  
3062 AspSerPheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGlu  
GACTCCTTCGATCCGCTTGTGGCGGAGGAGGACGAGCGGGAGATCTCCGTACCCGCAGAA  
CTGAGGAAGCTAGGCGAACACCGCCTCCTCTGCTCGCCCTCTAGAGGCATGGCGCTCTT  
3102 BGL2,

## FIGURE 11 - Page 6

IleL uArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyr  
 3122 ATCTGCGGAAGTCTCGGAGATTGCCCCAGGCCCTGCCCGTTTGGGCGCGGCCGACTAT  
 TAGGACGCCTTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGGCCTGATA  
 3149 ALWN1, 3170 EAG1 XMA3,  
 AsnProProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGly  
 3182 AACCCCCGCTAGTGGAGACGTGGAAAAAGCCCGACTACGAACCACCTGTGGTCCATGGC  
 TTGGGGGGCGATCACCTCTGCACCTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCG  
 3223 HGIE2, 3235 NCOI,  
 CysProLeuProProProLysSerProProValProProProArgLysLysArgThrVal  
 3242 TGCCCGCTTCCACCTCCAAAGTCCCTCCTGTGCCTCCGCCTCGGAAGAAGCGGACGGTG  
 ACGGGCGAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCAC  
 ValLeuThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGly  
 3302 GTCTCACTGAATCAACCCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGC  
 CAGGAGTGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCG  
 3338 SACI, 3352 HIND3,  
 SerSerSerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaPro  
 3362 AGCTCCTCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCGCCCT  
 TCGAGGAGTTGAAGCCGTAATGCCCGCTGTATGCTGTTGTAGGAGACTCGGGCGGGGA  
 SerGlyCysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGly  
 3422 TCTGGCTGCCCCCGACTCCGACGCTGAGTCTTCTCCATGCCCCCCTGGAGGGG  
 AGACCGACGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCC  
 3443 EAM11051,  
 GluProGlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsn  
 3482 GAGCTGGGGATCCGATCTTAGCGACGGGTGATGGTCAACGGTCAGTAGTGAGGCCAAC  
 CTCGGACCCCTAGGCCTAGAATCGCTGCCAGTACCAGTTGCCAGTCATCACTCCGGTTG  
 3490 BAMHI, 3491 BSAB1, 3493 BSPE1,  
 AlaGluAspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrPro  
 3542 GCGGAGGATGTCGTGTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCACCCCG  
 CGCTCCTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCTGAGCAGTGGGGC  
 3595 DRA3,  
 CysAlaAlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHis  
 3602 TGCGCCGCGGAAGAACAGAACTGCCCATCAATGCACTAAGCAACTCGTTGCTACGTCAC  
 ACGCGGCGCCTTCTTGTCTTTGACGGGTAGTTACGTGATTCGTTGAGCAACGATGCAGTG  
 3606 SAC2, 3617 ALWN1, 3661 PFLM1,  
 HisAsnLeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThr  
 3662 CACAATTTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAAGAAAGTCACA  
 GTGTTAAACCACATAAGGTGGTGGAGTCCGTACGAACGGTTTCCGTCTTCTTTCAGTGT  
 3687 DRA3,  
 PheAspArgLeuGlnValLeuAspS rHisTyrGlnAspValLeuLysGluValLysAla

## FIGURE 11 - Page 7

3722 TTTGACAGACTGCAAGTTCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCA  
AAACTGTCTGACGTTCAAGACCTGTCGGTAATGGTCCTGCATGAGTTCCTCCAATTTCTGT  
AlaAlaSerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrPro  
3782 GCGGCGTCAAAAGTGAAGGCTAACTTGCTATCCGTAGAGGAAGCTTGCAGCCTGACGCCC  
CGCCGCAGTTTTCTCACTTCCGATTGAACGATAGGCATCTCCTTCGAACGTCGGACTGCGGG  
3822 HIND3,  
ProHisSerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArg  
3842 CCACACTCAGCCAAATCCAAGTTTGCTTATGGGGCAAAGACGTCCGTTGCCATGCCAGA  
GGTGTGAGTCGGTTTAGGTTCAAACCAATACCCCGTTTTCTGCAGGCAACGGTACGGTCT  
3881 AAT2, 3896 BGLI,  
LysAlaValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrPro  
3902 AAGGCCGTAAACCCACATCAACTCCGTGTGGAAAGACCTTCTGGAAGACAATGTAACACCA  
TTCCGGCATTGGGTGTAGTTGAGGCACACCTTTCTGGAAGACCTTCTGTTACATTGTGGT  
IleAspThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGly  
3962 ATAGACACTACCATCATGGCTAAGAACGAGGTTTTCTGCGTTTCAGCCTGAGAAGGGGGGT  
TATCTGTGATGGTAGTACCGATTCTTGCTCCAAAAGACGCAAGTCGGACTCTTCCCCCA  
ArgLysProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMet  
4022 CGTAAGCCAGCTCGTCTCATCGTGTTCCTCGATCTGGGCGTGCGCGTGTGCGAAAAGATG  
GCATTCCGTCGAGCAGAGTAGCACAAGGGGCTAGACCCGCACGCGCACACGCTTTTCTAC  
AlaLeuTyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPhe  
4082 GCTTTGTACGACGTGGTTACAAAGCTCCCCTTGCCCGTGATGGGAAGCTCCTACGGATT  
CGAAACATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCCTTCGAGGATGCCTAAG  
GlnTyrSerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThr  
4142 CAATACTCACCAGGACAGCGGGTTGAATTCCTCGTGCAAGCGTGGAAGTCCAAGAAAACC  
GTTATGAGTGGTCCTGTGCCCCAACTTAAGGAGCACGTTTCGCACCTTCAGGTTCTTTTGG  
4166 ECORI,  
ProMetGlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIle  
4202 CCAATGGGGTTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATC  
GGTTACCCCAAGAGCATACTATGGGCGACGAACTGAGGTGTCAGTGACTCTCGCTGTAG  
4235 DRD1, 4242 ALWN1,  
ArgThrGluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIle  
4262 CGTACGGAGGAGGCAATCTACCAATGTTGTGACCTCGACCCCAAGCCCGCGTGCCATC  
GCATGCCTCCTCCGTTAGATGGTTACAACACTGGAGCTGGGGGTTCCGGCGCACCGGTAG  
4307 BGLI, 4314 BALI,  
LysSerLeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsn  
4322 AAGTCCCTCACCAGAGAGGCTTTATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAGAAC  
TTCAGGGAGTGGCTCTCCGAAATACAACCCCGGGGAGAATGGTTAAGTTCCCCCTCTTG  
4351 APAI,  
CysGlyTyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeu  
4382 TGCGGCTATCGCAGGTGCCGCGAGCGGCGTACTGACAACCTAGCTGTGGTAACACCTC

## FIGURE 11 - Page 8

ACGCCGATAGCGTCCACGGCGCGCTCGCCGCATGACTGTTGATCGACACCATTGTGGGAG

4442 ThrCysTyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMet  
 ACTTGCTACATCAAGGCCCGGGCAGCCTGTCGAGCCGCAGGGCTCCAGGACTGCACCATG  
 TGAACGATGTAGTTCCGGGCGCGTCGGACAGCTCGGCGTCCCGAGGTCTTGACGTGGTAC

4458 SMAI XMAI,

4502 LeuValCysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAla  
 CTCGTGTGTGGCGACGACTTAGTCGTTATCTGTGAAAGCGCGGGGTCCAGGAGGACGCG  
 GAGCACACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCCAGGTCTCTCGCG

4514 DRD1, 4517 TTH3I,

4562 AlaSerLeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspPro  
 GCGAGCCTGAGAGCCTTCACGGAGGCTATGACCAGGTACTCCGCCCCCTGGGGACCCC  
 CGCTCGGACTCTCGGAAGTGCTCCGATACTGGTCCATGAGGCGGGGGGACCCCTGGGG

4622 ProGlnProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAla  
 CCACAACCAGAAATACGACTTGGAGCTCATAACATCATGCTCTCCAACGTGTGAGTCGCC  
 GGTGTTGGTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTTGCACAGTCAGCGG

4643 SACI,

4682 HisAspGlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAla  
 CACGACGGCGCTGGAAAGAGGGTCTACTACCTCACCCTGACCCCTACAACCCCCCTCGCG  
 GTGCTGCCGCGACCTTTCTCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGGAGCGC

4737 NRUI,

4742 ArgAlaAlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIle  
 AGAGCTGCGTGGGAGACAGCAAGACACACTCCAGTCAATTCTGGCTAGGCAACATAATC  
 TCTCGACGCACCTCTGTGTTCTGTGTGAGGTCAGTTAAGGACCGATCCGTTGTATTAG

4802 MetPheAlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeu  
 ATGTTTGGCCCCACACTGTGGCGGAGGATGATACTGATGACCCATTTCTTTAGCGTCCTT  
 TACAAACGGGGGTGTGACACCCGCTCCTACTATGACTACTGGGTAAAGAAATCGCAGGAA

4812 PFLM1, 4813 DRA3,

4862 IleAlaArgAspGlnLeuGluGlnAlaLeuAspCysGluIleTyrGlyAlaCysTyrSer  
 ATAGCCAGGGACAGCTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCTGCTACTCC  
 TATCGGTCCCTGGTCAACTTGTCGGGAGCTAACGCTCTAGATGCCCGGACGATGAGG

4899 BGL2,

4922 IleGluProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSer  
 ATAGAACCCTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCA  
 TATCTTGGTGACCTAGATGGAGGTTAGTAAGTTTCTGAGGTACCGGAGTCGCGTAAAGT

4960 NCOI,

4982 LeuHisSerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGly  
 CTCCACAGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGATGCCTCAGAAAACCTGGG  
 GAGGTGTCAATGAGAGGTCCACTTTAGTTATCCACCGGCGTACGGAGTCTTTGAACCC

5021 SPHI, 5041 KPNI,

## FIGURE 11 - Page 9

5042 ValProProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAla  
GTACCGCCCTTGGGAGCTTGGAGACACCGGGCCCGGAGCGTCCGCGCTAGGCTTCTGGCC  
CRTGGCGGGAACGCTCGAACCTCTGTGGCCCGGGCCTCGCAGGCGCGATCCGAAGACCGG  
5070 APAI, 5097 BALI,  
ArgGlyGlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLys  
5102 AGAGGAGGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAG  
TCTCCTCCGTCCCGACGGTATACACCGTTTCATGGAGAAGTTGACCCGTCATTCTTGTTTC  
5119 NDEI,  
LeuLysLeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAla  
5162 CTCAAACCTCACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTCACGGCT  
GAGTTTGAGTGAGGTTATCGCCGGCGACCGGTTCGACCTGAACAGGCCGACCAAGTGCCGA  
5180 NOTI, 5181 EAGI XMA3, 5188 BALI, 5192 PVU2,  
GlyTyrSerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrp  
5222 GGCTACAGCGGGGAGACATTTATCACAGCGTGTCTCATGCCCCGCCCCGCTGGATCTGG  
CCGATGTCGCCCCCTCTGTAAATAGTGTGCACAGAGTACGGGCCGGGGCGACCTAGACC  
5246 DRA3,  
PheCysLeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgOP  
5282 TTTTGCTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCCAACCGATGAAGG  
AAAACGGATGAGGACGAACGACGTCCCATCCGTAGATGGAGGAGGGGTTGGCTACTTCC  
5301 PSTI, 5331 HGIE2,  
5342 TTGGGGTAAACACTCCGGCCTAAAAAAAAAAAAAAAAATCTAGAACCCGAGTCGAC  
AACCCCATTTGTGAGGCCGGATTTTTTTTTTTTTTTTAGATCTTGGGCTCAGCTG  
5378 XBAI, 5390 SALI,

FIGURE 12

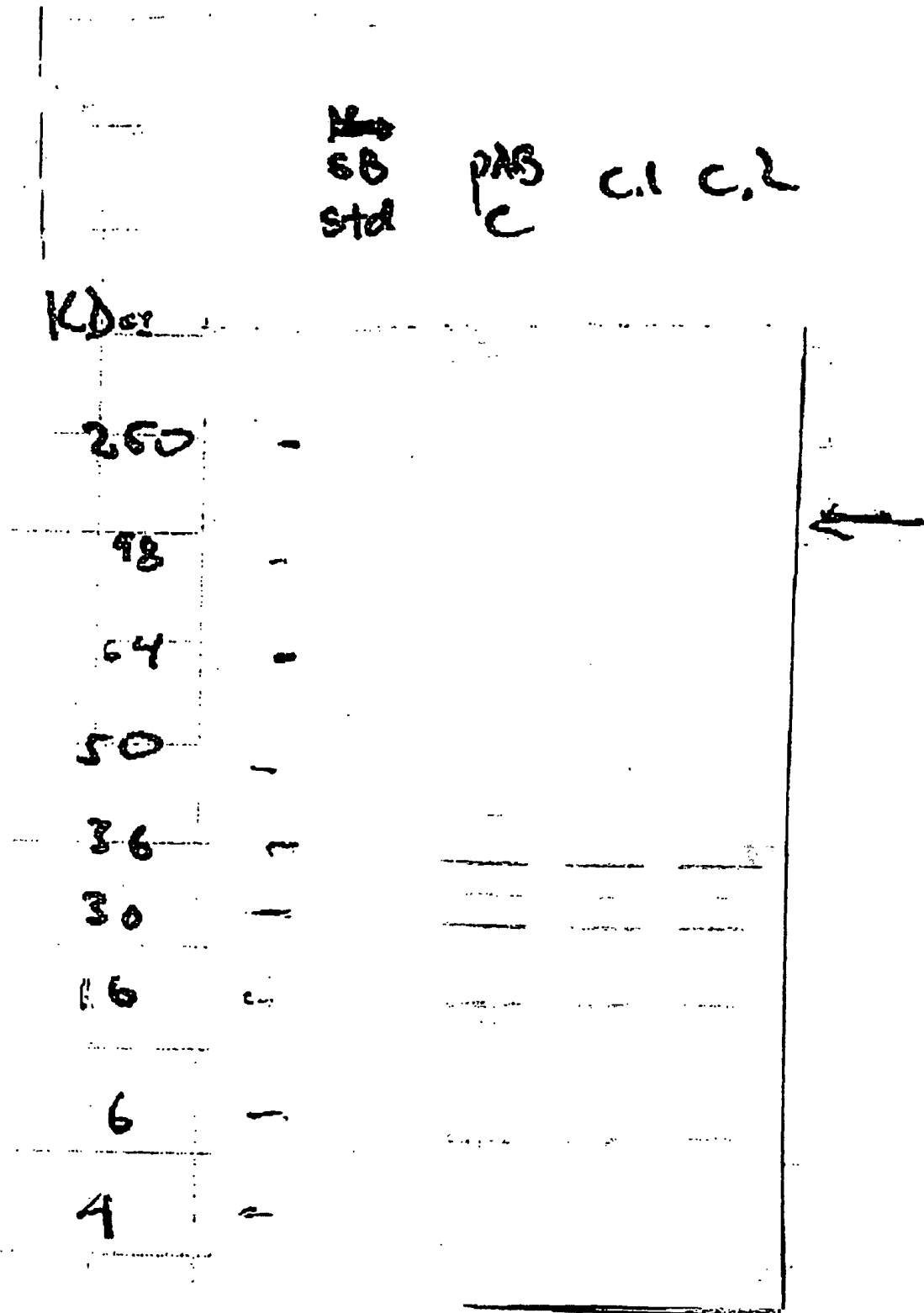
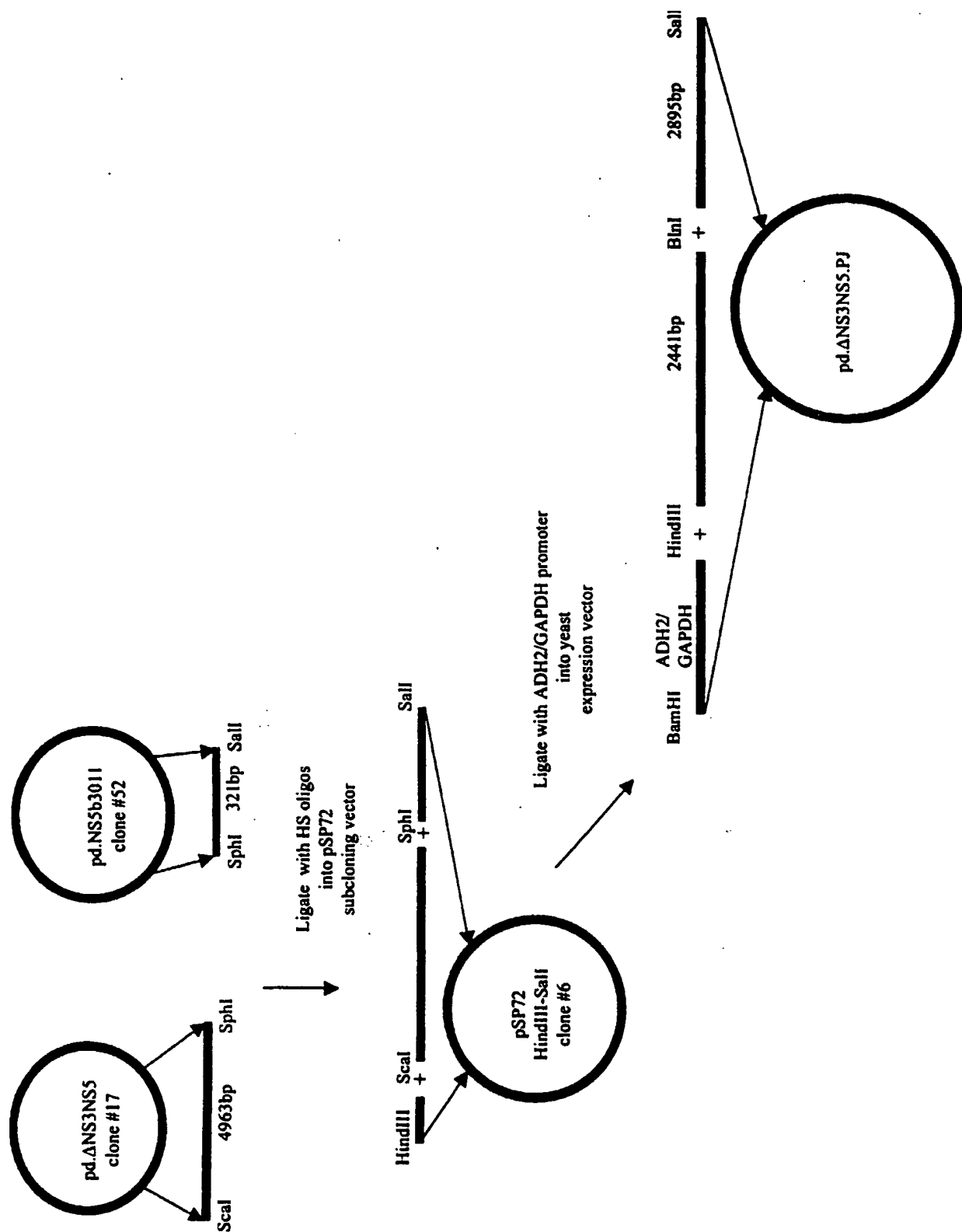


FIGURE 13



## FIGURE 14 - Page 1

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn  
 2 AGCTTACAAAACAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC  
 TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG  
 ^  
 1 HIND3, 24 NDEI, 52 SCAI,  
 ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp  
 62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT  
 GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCCTAGCTA  
 ^  
 116 CLAI,  
 ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr  
 122 CCTAACATCAGGACCGGGGTGAGAACAATTACCACTGGCAGCCCCATCACGTACTCCACC  
 GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGCATGAGGTGG  
 TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys  
 182 TACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT  
 ATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGGAATACTGTATTATTAAACA  
 AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln  
 242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA  
 CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAAGTGGTT  
 AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal  
 302 GCAGAGACTGCGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC  
 CGTCTCTGACGCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCCGAGGCAG  
 ^  
 303 ALWN1,  
 ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe  
 362 ACTGTGCCCCATCCCAACATCGAGGAGGTTGCTCTGTCCACCACCGGAGAGATCCCTTTT  
 TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA  
 TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis  
 422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTCTGTCTAT  
 ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA  
 SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal  
 482 TCAAAGAAGAAGTGCGACGAACCTCGCCGCAAAGCTGGTGCATTGGGCATCAATGCCGTG  
 AGTTTCTTCTTACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTACGGCAC  
 AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal  
 542 GCCTACTACGCGGTCTTGACGTGTCCGTCATCCCGACCAGCGCGCATGTTGTGTCGTGTCG  
 CGGATGATGGCGCCAGAACTGCACAGGCAGTAGGGCTGGTCCCGCTACAACAGCAGCAC  
 ^ ^  
 550 SAC2, 560 DRD1,  
 AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn  
 602 GCAACCGATGCCCTCATGACCGGCTATACGGCGACTTCGACTCGGTGATAGACTGCAAT  
 CGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTGACGTTA  
 ^  
 615 BSPH1.



## FIGURE 14 - Page 2

662 ACGTGTGTACCCAGACAGTCGATTTTCAGCCTTGACCCTACCTTCACCATTTGAGACAAATC  
 TGCACACAGTGGGTCTGTACGCTAAAGTCGGAAGTGGGATGGAAGTGGTAACCTCTCTTAC

ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys  
 722 ACAGGTCATCTACAGATTGTGGCAGCGGGGAGCGCCCTCCGGCATGTTCTGACTCGTCC  
 TGGCAGGGGGTTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCCTGACCGTCCCCCTTC

ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer  
 762 CCAGGCATCTACAGATTTGTGGCAGCGGGGAGCGCCCTCCGGCATGTTCTGACTCGTCC  
 GGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTGAGCAGG

816 BGLI, 833 DRD1,

ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr  
 842 GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCAGCCCCGCCGAGACT  
 CAGGAGACACTCAGGATACTGCGTCCGACACGAACCATACTCGAGTGCGGGCGGCTCTGA

881 SACI,

ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu  
 902 ACAGTTAGGCTACGAGCGTACATGAACACCCGGGGCTTCCCGTGTGCCAGGACCATCTT  
 TGTCATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCTTGTTAGAA

931 SMAI XMAI,

GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln  
 962 GAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCCACTTTCTATCCAG  
 CTTAAACCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC

985 STUI,

ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla  
 1022 ACAAGCAGAGTGGGGAGAACCTTCTTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT  
 TGTTTCGTCTACCCCTCTTGAAGGAATGGACCATCGCATGGTTCGGTGGCACACGCCA

1069 DRA3,

ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys  
 1082 AGGGCTCAAGCCCCTCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTGCGCTCAAG  
 TCCCGAGTTCGGGGAGGGGTAGCACCCCTGGTCTACACCTTCACAACTAAGCGGAGTTC

ProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsnGluIle  
 1142 CCCACCCTCCATGGGCCAACACCCCTGCTATACAGACTGGGCGCTGTTTCAATGAAATC  
 GGGTGGGAGGTACCCGGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTACTTTAG

1150 NCOI,

ThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeuGluVal  
 1202 ACCCTGACGCACCCAGTCACCAAATACATCATGACATGCATGTCGGCCGACCTGGAGGTC  
 TGGGACTGCGTGGGTGAGTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGACCTCCAG

1230 BSPH1, 1234 DRD1, 1237 AVA3, 1245 EAG1 XMA3, 1250 DRD1,

ValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyrCysLeu  
 1262 GTCACGAGCACCTGGGTGCTCGTTGGCGCGTCCTGGCTGCTTTGGCCGCGTATTGCCTG  
 CAGTGCTCGTGACCCACGACCAACCGCCGAGGACCGACGAAACCGGCGCATAACGGAC

## FIGURE 14 - Page 3

SerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAlaIleIle  
1322 TCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCGTCTTGTCCGGGAAGCCGGCAATCATA  
AGTTGTCCGACGCACCAAGTATCACCCGTCAGCAGAACAGGCCCTTCGGCCGTTAGTAT  
1369 NAEI,  
ProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGlnHisLeu  
1382 CCTGACAGGGAAGTCCTCTACCGAGAGTTCGATGAGATGGAAGAGTGCTCTCAGCACTTA  
GGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCACGAGAGTCGTGAAT  
1385 DRD1,  
ProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeuGlyLeu  
1442 CCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAGAAGGCCCTCGGCCCTC  
GGCATGTAGCTCGTTCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCCGGGAGCCGGAG  
LeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsnTrpGln  
1502 CTGCAGACCGCGTCCCGTCAGGCAGAGGTTATCGCCCTGCTGTCCAGACCAACTGGCAA  
GACGTCTGGCGCAGGGCAGTCCGTCTCAATAGCGGGGACGACAGGTCTGGTTGACCGTT  
1502 PSTI, 1507 TTH3I,  
LysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGlnTyrLeu  
1562 AAACGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAATACTTG  
TTTGAGCTCTGGAAGACCCGCTTCGTATACACCTGAAGTAGTCACCTATGTTATGAAC  
1565 XHOI, 1586 NDEI,  
AlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPheThrAla  
1622 GCGGGCTTGTCAACGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTTACAGCT  
CGCCCGAACAGTTGCGACGGACCATTTGGGGCGGTAACGAAGTAACACCGAAAATGTGCA  
1643 BSTE2, 1677 ALWN1 PVU2,  
AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp  
1682 GCTGTACACAGCCCACTAACCCTAGCCAAACCCTCCTCTTCAACATATTGGGGGGGTGG  
CGACAGTGGTGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC  
ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla  
1742 GTGGCTGCCAGCTCGCCGCCCCCGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT  
CACCGACGGGTCGAGCGGGCGGGGCCACGGCGATGACGGAAACACCCGCGACCGAATCGA  
1794 ESP1,  
GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr  
1802 GGCGCCGCCATCGGCAGTGTTGGACTGGGGAAGGTCCTCATAGACATCCTTGCAGGGTAT  
CCGCGGCGGTAGCCGTCACAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCCAT  
1802 KAS1 NARI,  
GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer  
1862 GGCGCGGGCGTGGCGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCTCC  
CCGCGCCCGCACCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG  
1878 SACI, 1899 BSPH1,

## FIGURE 14 - Page 4

ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly  
 1922 ACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCGTAGTCGGC  
 TGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCATCAGCCG  
 ^  
 1928 TTH3I,  
 ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp  
 1982 GTGGTCTGTGCAGCAATACTGCCCGGCACGTTGGCCCGGCGAGGGGGCAGTGCAGTGG  
 CACCAGACACGTCGTTATGACGCGCGCGTGCAACCGGGCCCGTCCCCCGTCACGTCAAC  
 ^ ^  
 2004 NAEI, 2017 SMAI XMAI,  
 MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal  
 2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTCCCCACGCACTACGTG  
 TACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGGTGCGTGATGCAC  
 ^ ^  
 2067 SMAI XMAI, 2093 DRA3,  
 ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln  
 2102 CCGGAGAGCGATGCAGCTGCCCGCGTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG  
 GGCCTCTCGCTACGTGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACATTGGGTC  
 ^ ^  
 2115 PVU2, 2159 ALWN1,  
 LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer  
 2162 CTCCTGAGGCGACTGCACCAGTGGATAAGCTCGGAGTGTAACCTCCATGCTCCGGTTCC  
 GAGGACTCCGCTGACGTGGTCACCTATTTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG  
 ^ ^  
 2164 MST2, 2220 ECON1,  
 TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu  
 2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACCTGGCTA  
 ACCGATTCCCTGTAGACCCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGGACCGAT  
 ^ ^  
 LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr  
 2292 AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCTTTGTGTCTGCCAGCGCGGTAT  
 TTTTCGATTTCGAGTACGGTGTGACGGACCCCTAGGGGAAACACAGGACGGTCGCGCCCAT  
 ^ ^  
 2285 ESP1, 2300 PVU2, 2310 BAMHI,  
 LysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAlaGluIle  
 2342 AAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC  
 TTCCCCAGACCGCTCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG  
 ^ ^  
 ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet  
 2402 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCCGTCTAGGACCTGCAGGAACATG  
 TGACCTGTACAGTTTTTGCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCCTTGATC  
 ^ ^  
 2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,  
 TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla  
 2462 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCCGTACCCCCCTTCCTGCG  
 ACCTCACCTGGAAGGGGTAATTACGGATGTGGTGCCCGGGGACATGGGGGGAAGGACGC  
 ^ ^  
 2480 ASE1, 2497 APAI,  
 ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln

## FIGURE 14 - Page 5

2522 CCGAACTACACGTTTCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATAAGGCAG  
GGCTTGATGTGCAAGCGCGATACCTCCACAGACGTCTCCTTATGCACCTCTATTCCGTC

2553 PSTI,

2582 ValGlyAspPheHisTyrValThrGlyMetThrThrAspAsnLeuLysCysProCysGln  
GTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCGTGCCAG  
CACCCCTGAAGGTGATGCACTGCCCATCTGATGACTGTTAGAATTTACGGGCACGGTC

2594 DRA3,

2642 ValProSerProGluPhePheThrGluLeuAspGlyValArgLeuHisArgPheAlaPro  
GTCCCATCGCCGAATTTTTCACAGAATTGGACGGGGTGCGCCTACATAGGTTTGCGCC  
CAGGGTAGCGGGCTTAAAAAGTGTCTTAACCTGCCCCACGCGGATGTATCCAAACGCGGG

2702 ProCysLysProLeuLeuArgGluGluValSerPheArgValGlyLeuHisGluTyrPro  
CCCTGCAAGCCCTTGCTGCGGGAGGAGGTATCATTACAGAGTAGGACTCCACGAATACCCG  
GGGACGTTTCGGGAACGACGCCCTCCTCCATAGTAAGTCTCATCCTGAGGTGCTTATGGGC

2757 HGIE2,

2762 ValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSerMetLeu  
GTAGGGTCGCAATTACCTTGCGAGCCCGAACCGGACGTGGCCGTGTTGACGTCCATGCTC  
CATCCCAGCGTTAATGGAACGCTCGGGCTTGGCCTGCACCGGCACAACGAGGTACGAG

2809 AAT2,

2922 ThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGlySerPro  
ACTGATCCCTCCCATATAACAGCAGAGGCGCGCCGGCGAAGGTTGGCGAGGGGATCACCC  
TGACTAGGGAGGGTATATTGTCGTCTCCGCGGCGCGCTTCCAACCGCTCCCTAGTGGG

2850 EAG1 XMA3,

2982 ProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAlaThrCys  
CCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCAACTTGC  
GGGAGACACCGGTCGAGGAGCCGATCGGTTCGATAGGCGAGGTAGAGAGTTCCGTTGAACG

2889 BALI, 2903 NHEI,

2942 ThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuLeuTrpArgGln  
ACCGCTAACCATGACTCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAG  
TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGTTGGAGGATACCTCCGTC

2966 ESp1, 2969 SACI,

3002 GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer  
GAGATGGGCGGCAACATCACCGGGTTGAGTCAGAAAACAAAGTGGTGATTCTGGACTCC  
CTCTACCCGCCGTTGTAGTGGTCCCAACTCAGTCTTTTGTTCACCACTAAGACCTGAGG

3062 PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu  
TTCGATCCGCTTGTGGCGGAGGAGGACGAGCGGGAGATCTCCGTACCCGAGAAATCCTG  
AAGCTAGGCGAACACCGCTCCTCCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC

3096 BGL2,

3122 ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro  
CGGAAGTCTCGGAGATTGCCCGAGGCCCTGCCCGTTTGGGCGCGGCCGACTATAACCCC

## FIGURE 14 - Page 6

GCCTTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGGCCTGATATTGGGG  
 3143 ALWN1, 3164 EAG1 XMA3,  
 ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro  
 3182 CCGCTAGTGGAGACGTGGAAAAAGCCCGACTACGAACACCTGTGGTCCATGGCTGCCCG  
 GCGATCACCTCTGCACCTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCGACGGGC  
 3217 HGIE2, 3229 NCOI,  
 LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu  
 3242 CTTCCACCTCCAAAGTCCCCTCCTGTGCCTCCGCCTCGGAAGAAGCGGACGGTGGTCCTC  
 GAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCACCAGGAG  
 ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSer  
 3302 ACTGAATCAACCCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGCAGCTCC  
 TGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCGTCGAGG  
 3332 SACI, 3346 HIND3,  
 SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly  
 3362 TCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCCGCCCTTCTGGC  
 AGTTGAAGGCCGTAATGCCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG  
 CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluPro  
 3422 TGCCCCCGGACTCCGACGCTGAGTCCTATTCTCCATGCCCCCCTGGAGGGGGAGCCT  
 ACGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA  
 3437 EAM11051,  
 GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu  
 3482 GGGGATCCGGATCTTAGCGACGGGTCAATGCAACGGTCAGTAGTGAGGCCAACGCGGAG  
 CCCCTAGGCCTAGAATCGCTGCCCAGTACCAGTTGCCAGTCATCACTCCGTTGCGCCTC  
 3484 BAMHI, 3485 BSAB1, 3487 BSP1,  
 AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla  
 3542 GATGTCGTGTGCTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCACCCCGTGCGCC  
 CTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCGTGAGCAGTGGGGCACGCGG  
 3589 DRA3, 3600 SAC2,  
 AlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHisHisAsn  
 3602 GCGGAAGAACAGAACTGCCCATCAATGCACTAAGCAACTCGTTGCTACGTACCCACAAT  
 CGCCTTCTTGCTTTGACGGGTAGTTACGTGATTCTGTTGAGCAACGATGCAGTGGTGTTA  
 3611 ALWN1, 3655 PFLM1,  
 LeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThrPheAsp  
 3662 TTGGTGTATTCCACCACCTCAGCAGTGCTTGCCAAAGGCAGAAAGTCACATTTGAC  
 AACCACATAAGGTGGTGGAGTGCGTCACGAACGGTTTCCGTCTTCTTTCAGTGAAACTG  
 3681 DRA3,  
 ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla  
 3722 AGACTGCAAGTTCTGGACAGCCATTACAGGACGTAAGGAGGTTAAAGCAGCGCGG  
 TCTGACGTTCAAGACCTGTCGGTAATGGTCCTGCATGAGTTCCTCAATTTCTGTCGCCG

## FIGURE 14 - Page 7

SerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrProProHis  
 3782 TCAAAAGTGAAGGCTAACTTGCTATCCGTAGAGGAAGCTTGCAGCCTGACGCCCCACAC  
 AGTTTTCACTTCCGATTGAACGATAGGCATCTCCTTCGAACGTGGACTCGGGGGGTGTG  
 3816 HIND3,  
 SerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArgLysAla  
 3942 TCAGCCAAATCCAAGTTTGGTTATGGGGCAAAGACGTCCGTTGCCATGCCAGAAAGGCC  
 AGTCGGTTTAGGTTCAAACCAATACCCCGTTTTCTGCAGGCAACGGTACGGTCTTTCCGG  
 3875 AAT2, 3890 BGLI,  
 ValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrProIleAsp  
 3902 GTAACCCACATCAACTCCGTGTGGAAAGACCTTCTGGAAGACAATGTAAACCAATAGAC  
 CATTGGGTGTAGTTGAGGCACACCTTTCTGGAAGACCTTCTGTTACATTGTGGTTATCTG  
 ThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGlyArgLys  
 3962 ACTACCATCATGGCTAAGAACGAGGTTTTCTGCGTTTCAGCCTGAGAAGGGGGTTCGTAAG  
 TGATGGTAGTACCGATTCTTGCTCCAAAGACGCAAGTCGGACTCTTCCCCCAGCATTG  
 ProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMetAlaLeu  
 4022 CCAGCTCGTCTCATCGTGTTCCTCCCGATCTGGGCGTGCGCGTGTGCGAAAAGATGGCTTTG  
 GGTGAGCAGAGTAGCACAAAGGGGCTAGACCCGCACGCGCACAGCTTTTCTACCGAAAC  
 TyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPheGlnTyr  
 4082 TACGACGTGGTTACAAAGCTCCCCCTTGCCCGTGATGGGAAGCTCCTACGGATTCCAATAC  
 ATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCCTTCGAGGATGCCTAAGGTTATG  
 SerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThrProMet  
 4142 TCACCAGGACAGCGGGTTGAATTCCTCGTGCAAGCGTGGAAGTCCAAGAAAACCCCAATG  
 AGTGGTCTGTGCGCCCACTTAAGGAGCACGTTGCGACCTTCAGGTTCTTTTGGGGTTAC  
 4160 ECORI,  
 GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr  
 4202 GGGTTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATCCGTACG  
 CCAAGAGCATACTATGGGCGACGAACTGAGGTGTCAGTCACTCTCGCTGTAGGCATGC  
 4229 DRD1, 4236 ALWN1,  
 GluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIleLysSer  
 4262 GAGGAGGCAATCTACCAATGTTGTGACCTCGACCCCCAAGCCCCGCTGGCCATCAAGTCC  
 CTCCTCCGTTAGATGGTTACAACACTGGAGCTGGGGGTTTCGGGCGCACCGGTAGTTCAGG  
 4301 BGLI, 4308 BALI,  
 LeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsnCysGly  
 4322 CTCACCGAGAGGCTTTATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAGAAGTGGCGC  
 GAGTGGCTCTCCGAAATACAACCCCGGGAGAATGGTTAAGTTCCCCCTCTTGACGCCG  
 4345 APAI,  
 TyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys  
 4382 TATCGCAGGTGCCGCGAGCGGCGTACTGACAACTAGCTGTGGTAACACCCTCACTTGC  
 ATAGCGTCCACGGCGCGCTCGCCGCATGACTGTTGATCGACACCATTGTGGGAGTGAACG

## FIGURE 14 - Page 8

TyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMetLeuVal  
 4442 TACATCAAGGCCCGGGCAGCCTGTCGAGCCGCAGGGCTCCAGGACTGCACCATGCTCGTG  
 ATGTAGTTCCGGGCCCGTCGGACAGCTCGGCGTCCCGAGGTCCTGACGTGGTACGAGCAC  
 ^  
 4452 SMAI XMAI,  
 CysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAlaAlaSer  
 4502 TGTGGCGACGACTTAGTCGTTATCTGTGAAAGCGCGGGGGTCCAGGAGGACGCGGCGAGC  
 ACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCCAGGTCCTCTGCGCCGCTCG  
 ^ ^  
 4508 DRD1, 4511 TTH3I,  
 LeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspProProGln  
 4562 CTGAGAGCCTTCACGGAGGCTATGACCAGGTACTCCGCCCCCCTGGGGACCCCCACAA  
 GACTCTCGGAAGTGCCTCCGATACTGGTCCATGAGGCGGGGGGACCCTGGGGGGTGT  
 ProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAlaHisAsp  
 4622 CCAGAATACGACTTGGAGCTCATAACATCATGCTCCTCCAACGTGTCAGTCGCCCACGAC  
 GSTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTTGCACAGTCAGCGGGTGTG  
 ^  
 4637 SACI,  
 GlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAlaArgAla  
 4682 GCGCTGGAAAGAGGGTCTACTACCTACCCGTGACCCTACAACCCCCCTCGCGAGAGCT  
 CCGCGACCTTTCTCCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGGAGCGCTCTCGA  
 ^  
 4731 NRUI,  
 AlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIleMetPhe  
 4742 GCGTGGGAGACAGCAAGACACACTCCAGTCAATTCCTGGCTAGGCAACATAATCATGTTT  
 CGCACCTCTGTCGTTCTGTGTGAGGTCAGTTAAGGACCGATCCGTTGTATTAGTACAAA  
 AlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeuIleAla  
 4802 GCCCCACACTGTGGGCGAGGATGATACTGATGACCCATTTCTTTAGCGTCCTTATAGCC  
 CGGGGGTGTGACACCCGCTCCTACTATGACTACTGGGTAAAGAAATCGCAGGAATATCGG  
 ^ ^  
 4806 PFLM1, 4807 DRA3,  
 ArgAspGlnLeuGluGlnAlaLeuAspCysGluIleTyrGlyAlaCysTyrSerIleGlu  
 4862 AGGGACCAGCTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCTGCTACTCCATAGAA  
 TCCCTGGTCAACTTGTCCGGGAGCTAACGCTCTAGATGCCCCGACGATGAGGTATCTT  
 ^  
 4893 BGL2,  
 ProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSerLeuHis  
 4922 CCACTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCACTCCAC  
 GGTGACCTAGATGGAGGTTAGTAAGTTTCTGAGGTACCGGAGTCGCGTAAAAGTGAGGTG  
 ^  
 4954 NCOI,  
 SerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGlyValPro  
 4982 AGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGCATGCCTCAGAAAACCTGGGGTACCG  
 TCAATGAGAGGTCCACTTTAGTTATCCACCGGCGTACGGAGTCTTTGAACCCCATGGC  
 ^ ^  
 5015 SPHI, 5035 KPNI,  
 ProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAlaArgGly

## FIGURE 14 - Page 9

5042 CCCTTGCGAGCTTGGAGACACCGGGCCCGAGCGTCCGCGCTAGGCTTCTGGCCAGAGGA  
 GGAACGCTCGAACCTCTGTGGCCCGGCTCGCAGGCGCGATCCGAAGACCGSTCTCCT  
 5064 APAI, 5091 BALI,  
 GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys  
 5102 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAGCTCAAA  
 CCGTCCCGACGGTATACACCGTTCATGGAGAAGTTGACCCGTCATTCTTGTTCGAGTTT  
 5113 NDEI,  
 LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr  
 5162 CTCACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTCACGGCTGGCTAC  
 GAGTGAGGTTATCGCCGGCGACCGGTCGACCTGAACAGGCCGACCAAGTGCCGACCGATG  
 5174 NOTI, 5175 EAGI XMA3, 5182 BALI, 5186 PVU2,  
 SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys  
 5222 AGCGGGGGAGACATTTATCACAGCGTGTCTCATGCCCGGCCCGCTGGATCTGGTTTTGC  
 TCGCCCCCTCTGTAAATAGTGTGCGACAGAGTACGGGCCGGGGCGACCTAGACCAAAACG  
 5240 DRA3,  
 LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgOP  
 5282 CTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCAACCGATGAATAGTCGAC  
 GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTTGGCTACTTATCAGCTG  
 5295 PSTI, 5336 SALI,



**FIGURE 15**



FIGURE 16 - Page 1

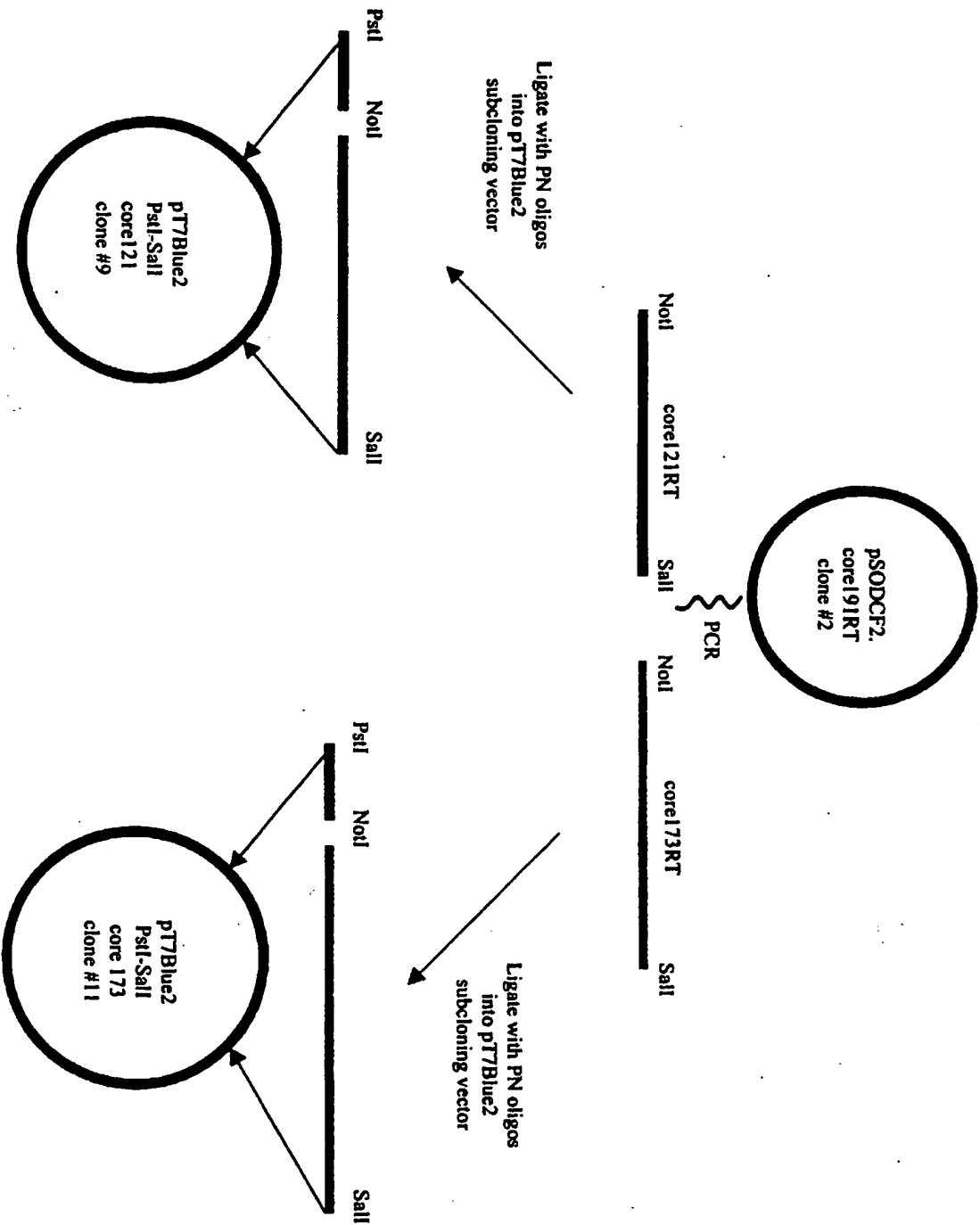
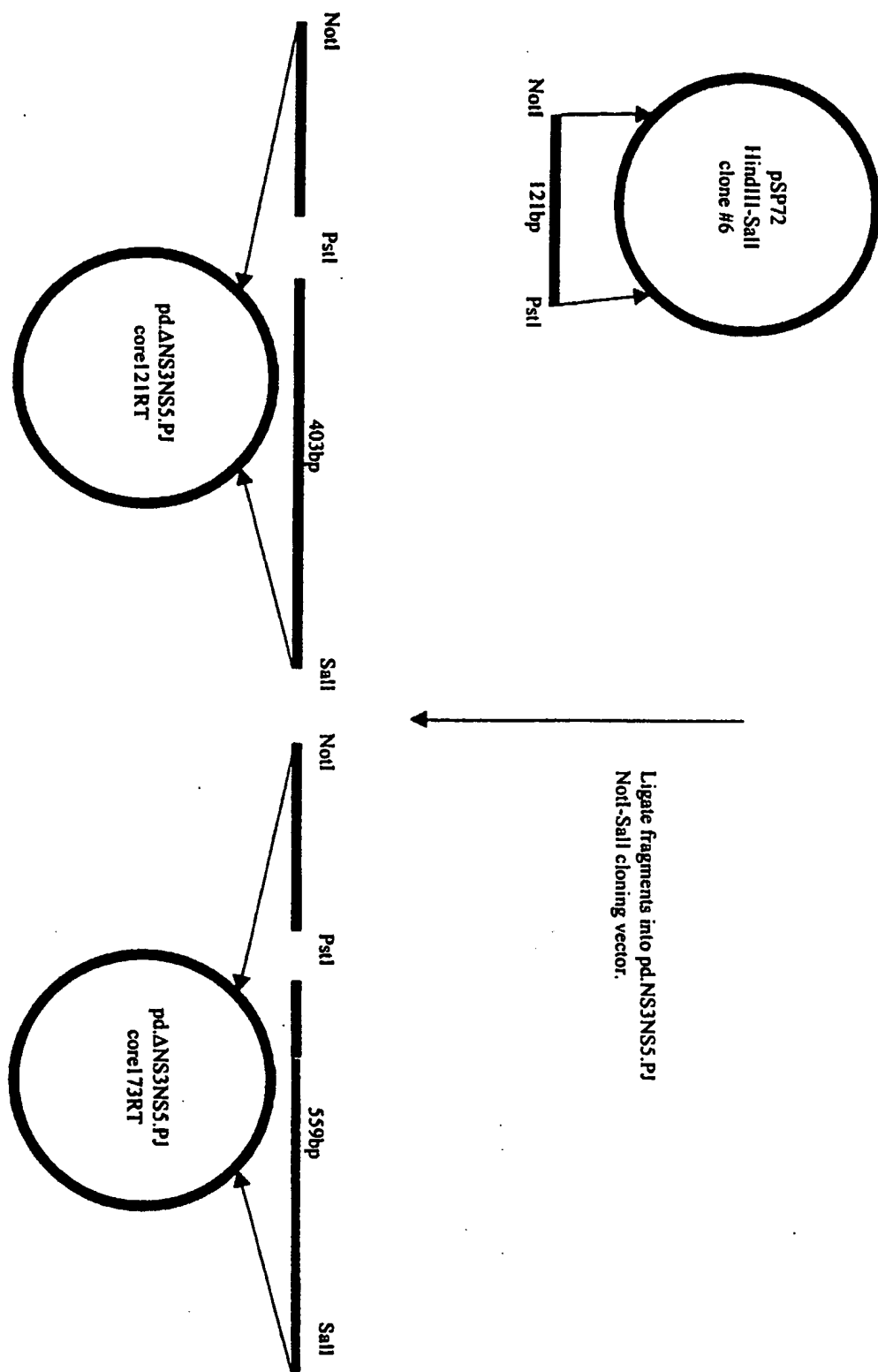


FIGURE 16 - Part 2



## FIGURE 17 - Page 1

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn  
 2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC  
 TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG  
 ^  
 1 HIND3, 24 NDEI, 52 SCAI,  
 ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp  
 62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT  
 GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCCTAGCTA  
 ^  
 116 CLAI,  
 ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr  
 122 CCTAACATCAGGACCGGGGTGAGAACAATTACCACTGGCAGCCCCATCACGTACTCCACC  
 GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGCATGAGGTGG  
 TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys  
 182 TACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT  
 ATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGCAATACTGTATTATTAAACA  
 AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln  
 242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA  
 CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAAGTGGTT  
 AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal  
 302 GCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC  
 CGTCTCTGACGCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCGAGGCAG  
 ^  
 303 ALWN1,  
 ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe  
 362 ACTGTGCCCCATCCCAACATCGAGGAGGTTGCTCTGTCCACCACCGAGAGATCCCTTTT  
 TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA  
 TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis  
 422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTCTGTCAT  
 ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA

## FIGURE 17 - Page 2

SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal  
482 TCAAAGAAGAAGTGCACGAACTCGCCGCAAAGCTGGTCGCATTGGGCATCAATGCCGTG  
AGTTTCTTCTTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTACGGCAC

AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal  
542 GCCTACTACCGCGTCTTGACGTGTCCGTTCATCCCGACCAGCGGCGATGTTGTCGTCTGTG  
CGGATGATGGCGCCAGAACTGCACAGGCAGTAGGGCTGGTCGCCGCTACAACAGCAGCAC

550 SAC2, 560 DRD1,

AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn  
602 GCAACCGATGCCCTCATGACCGGTATACCGCGACTTCGACTCGGTGATAGACTGCAAT  
CGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTGACGTTA

615 BSPH1,

ThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGluThrIle  
662 ACGTGTGTCACCCAGACAGTCGATTTCAGCCTTGACCCTACCTTCACCATTGAGACAATC  
TGCACACAGTGGGTCTGTCTAGCTAAAGTCGGAAC TGGGATGGAAGTGGAAC TCTGTTAG

ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys  
722 ACGTCCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGGGGGAAG  
TGCGAGGGGGTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCCTGACCGTCCCCCTTC

ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer  
782 CCAGGCATCTACAGATTTGTGGCACCAGGGGAGCGCCCTCCGGCATGTTGCACTCGTCC  
GGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTGAGCAGG

816 BGLI, 833 DRD1,

ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr  
842 GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCGCCGAGACT  
CAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAGTGCGGGCGGCTCTGA

881 SACI,

ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu  
902 ACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGACCATCTT  
TGTCAATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCCTGGTAGAA

931 SMAI XMAI,

GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln  
962 GAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCCACTTTCTATCCAG  
CTTAAACCCCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC

985 STUI,

ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla  
1022 ACAAGCAGAGTGGGGAGAACCTTCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT  
TGTTTCGTCTACCCCTCTTGAAGGAATGGACCATCGCATGGTTCCGGTGGCACACGCGA

1069 DRA3,

ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys  
1082 AGGGCTCAAGCCCCCTCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTGCGCTCAAG

## FIGURE 17 - Page 3

TCCCGAGTTCGGGGAGGGGGTAGCACCCCTGGTCTACACCTTCACAACTAAGCGGAGTTC

ProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsnGluIle  
 1142 CCCACCCTCCATGGGCCAACCCCCTGCTATACAGACTGGGCGCTGTTTCTAGAATGAAATC  
 GGGTGGGAGGTACCCGGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTACTTTAG  
 ^  
 1150 NCOI,

ThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeuGluVal  
 1202 ACCCTGACGCACCCAGTCACCAAATACATCATGACATGCATGTCGGCCGACCTGGAGGTC  
 TGGGACTGCGTGGGTGAGTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGACCTCCAG  
 ^ ^ ^ ^ ^  
 1230 BSPH1, 1234 DRD1, 1237 AVA3, 1245 EAG1 XMA3, 1250 DRD1,

ValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyrCysLeu  
 1262 GTCACGAGCACCTGGGTGCTCGTTGGCGGCGTCTGGCTGCTTTGGCCGCGTATTGCCCTG  
 CAGTGCTCGTGGACCCACGAGCAACCGCCGAGGACCGACGAAACCGCGCATAACGGAC

SerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAlaIleIle  
 1322 TCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCTGCTTGTCCGGGAAGCCGGCAATCATA  
 AGTTGTCCGACGCACCACTATCACCCGTCCAGCAGAACAGGCCCTTCGGCCGTTAGTAT  
 ^  
 1369 NAEI,

ProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGlnHisLeu  
 1382 CCTGACAGGGAAGTCTCTACCGAGAGTTCGATGAGATGGAAGAGTGCTCTCAGCACTTA  
 GGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCACGAGAGTCGTGAAT  
 ^  
 1385 DRD1,

ProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeuGlyLeu  
 1442 CCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAGAAGCCCTCGGCCCTC  
 GGCATGTAGCTCGTTCCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCCGGGAGCCGGAG

LeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsnTrpGln  
 1502 CTGCAGACCGCGTCCCGTCAGGCAGAGGTTATCGCCCTGCTGTCCAGACCACTGGCAA  
 GACGTCTGGCGCAGGGCAGTCCGTCTCCAATAGCGGGGACGACAGGTCTGGTTGACCGTT  
 ^ ^  
 1502 PSTI, 1507 TTH3I,

LysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGlnTyrLeu  
 1562 AAATCTGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAATACTTG  
 TTTGAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCCTATGTTATGAAC  
 ^ ^  
 1565 XHOI, 1586 NDEI,

AlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPheThrAla  
 1622 GCGGGCTTGTCACGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTTACAGCT  
 CGCCGGAACAGTTGCGACGGACATTGGGGCGGTAACGAAGTAACTACCGAAAATGTCTGA  
 ^  
 1643 BSTE2, 1677 ALWN1 PVU2,

AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp  
 1682 GCTGTCAACAGCCCACTAACCCTAGCCAAACCTCCTTCAACATATTGGGGGGGTGG  
 CGACAGTGGTCGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC

## FIGURE 17 - Page 4

ValAlaAlaGlnL uAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla  
 1742 GTGGCTGCCCAGCTCGCCGCCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT  
 CACCGACGGGTCGAGCGGGGGGCCACGGCGATGACGGAAACACCCGCGACCGAATCGA  
 1794 ESP1,  
 GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr  
 1802 GGCGCCGCCATCGGCAGTGTGGACTGGGGAAGGTCTCATAGACATCCTTGCAGGGTAT  
 CCGCGGCGGTAGCCGTCACAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCCAT  
 1802 KAS1 NARI,  
 GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer  
 1862 GGCGCGGGCGTGGCGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCTCC  
 CCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG  
 1878 SACI, 1899 BSPH1,  
 ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly  
 1922 ACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCGTAGTCGGC  
 TGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCTCGGGAGCATCAGCCG  
 1928 TTH3I,  
 ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp  
 1982 GTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCCGGCGAGGGGGCAGTGCAGTGG  
 CACCAGACACGTCGTTATGACGCGGCCGTGCAACCGGGCCCGCTCCCCCGTCACGTCACC  
 2004 NAEI, 2017 SMAI XMAI,  
 MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal  
 2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTCCCCCAGCCTACGTC  
 TACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGTGCGTGATGCAC  
 2067 SMAI XMAI, 2093 DRA3,  
 ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln  
 2102 CCGGAGAGCGATGCAGCTGCCCGCGTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG  
 GGCCTCTCGCTACGTGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACATTGGGTC  
 2115 PVU2, 2159 ALWN1,  
 LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer  
 2162 CTCCTGAGGCGACTGCACCAGTGGATAAGCTCGGAGTGTACCACTCCATGCTCCGGTTCC  
 GAGGACTCCGCTGACGTGGTCACCTATTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG  
 2164 MST2, 2220 ECON1,  
 TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu  
 2222 TGGCTAAGGGACATCTGGGACTGGATATCGGAGGTGTTGAGCGACTTTAAGACCTGGCTA  
 ACCGATTCCCTGTAGACCTTGACCTATACGCTCCACAACCTCGCTGAAATCTGGACCGAT  
 LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr  
 2282 AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCCTTTGTGTCCTGCCAGCGCGGGTAT  
 TTTGATTTCGAGTACGGTGTGACGGACCCTAGGGGAAACACAGGACGGTTCGCGCCCAT  
 2285 ESP1, 2300 PVU2, 2310 BAMHI,

## FIGURE 17 - Page 5

LysGlyValTrpArgGlyAspGlyIle MetHisThrArgCysHisCysGlyAlaGluIle  
 2342 AAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC  
 TTCCCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG

ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet  
 2402 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCCTAGGACCTGCAGGAACATG  
 TGACCTGTACAGTTTTTGGCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCTTGATC  
 2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,

TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla  
 2462 TGGAGTGGGACCTTCCCCATTAATGCCCTACACCACGGGCCCTGTACCCCTTCTCTGCG  
 ACCTCACCTGGAAGGGTAATTACGGATGTGGTGGCCGGGACATGGGGGAAGGACGC  
 2480 ASE1, 2497 APAI,

ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln  
 2522 CCGAATACACGTTTCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATAAGGCAG  
 GGCTTGATGTGCAAGCGCGATACCTCCACAGACGTCTCCTTATGCACCTCTATTCCGTC  
 2553 PSTI,

ValGlyAspPheHisTyrValThrGlyMetThrThrAspAsnLeuLysCysProCysGln  
 2582 GTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCGTGCCAG  
 CACCCCTGAAGGTGATGCACTGCCCATCTGATGACTGTTAGAATTTACGGGCACGGTC  
 2594 DRA3,

ValProSerProGluPhePheThrGluLeuAspGlyValArgLeuHisArgPheAlaPro  
 2642 GTCCCATCGCCGAATTTTTCACAGAATTGGACGGGGTGCGCCTACATAGGTTTGCGCCC  
 CAGGGTAGCGGGCTTAAAAGTGTCTTAACCTGCCCCACGCGGATGTATCCAAACGCGGG

ProCysLysProLeuLeuArgGluGluValSerPheArgValGlyLeuHisGluTyrPro  
 2702 CCCTGCAAGCCCTTGCTGCGGGAGGAGGTATCATTAGAGTAGGACTCCACGAATACCCG  
 GGGACGTTTCGGGAACGACGCCCTCCTCCATAGTAAGTCTCATCCTGAGGTGCTTATGGGC  
 2757 HGIE2,

ValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSerMetLeu  
 2762 GTAGGGTCGCAATTACCTTGCAGCCCCAACCGGACGTGGCCGTGTTGACGTCCATGCTC  
 CATCCAGCGTTAATGGAACGCTCGGGCTTGGCCTGCACCGGCACAACCTGCAGGTACGAG  
 2809 AAT2,

ThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGlySerPro  
 2822 ACTGATCCCTCCCATATAACAGCAGAGGCGCGGGCGAAGGTTGGCGAGGGGATCACCC  
 TGACTAGGGAGGGTATATTGTCGTCTCCGCGGCGCCGCTTCCAACCGCTCCCTAGTGGG  
 2850 EAG1 XMA3,

ProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAlaThrCys  
 2882 CCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCAACTTGC  
 GGGAGACACCGGTCGAGGAGCCGATCGGTCGATAGGCGAGGTAGAGAGTTCCGTTGAACG  
 2889 BALI, 2903 NHEI,



## FIGURE 17 - Page 6

ThrAlaAsnHisAspSerProAspAlaGluLeuIle GluAlaAsnLeuLeuTrpArgGln  
 2942 ACCGCTAACCATGACTCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAG  
 TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGGTTGGAGGATACCTCCGTC  
 ^ ^  
 2966 ESP1, 2969 SACI,  
 GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer  
 3002 GAGATGGGCGGCAACATCACCAGGGTTGAGTCAGAAAACAAAGTGGTGATTCTGGACTCC  
 CTCTACCCGCCGTTGTAGTGGTCCCAACTCAGTCTTTTGTTCACCACTAAGACCTGAGG  
 PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu  
 3062 TTCGATCCGCTTGTGGCGGAGGAGGACGAGCGGGAGATCTCCGTACCCGCAGAAATCCTG  
 AAGCTAGGCGAACACCGCCTCCTCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC  
 ^  
 3096 BGL2,  
 ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro  
 3122 CGGAAGTCTCGGAGATTCGCCCAGGCCCTGCCGTTTGGGCGCGGCCGACTATAACCCC  
 GCCTTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGCCTGATATTGGGG  
 ^ ^  
 3143 ALWN1, 3164 EAG1 XMA3,  
 ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro  
 3182 CCGCTAGTGGAGACGTGGAAAAAGCCCGACTACGAACCACCTGTGGTCCATGGCTGCCCG  
 GGGGATCACCTCTGCACCTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCGACGGGC  
 ^ ^  
 3217 HGIE2, 3229 NCOI,  
 LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu  
 3242 CTTCCACCTCCAAAGTCCCTCCTGTGCCTCCGCCTCGGAAGAAGCGGACGGTGGTCTC  
 GAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCACAGGAG  
 ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSer  
 3302 ACTGAATCAACCCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGCAGCTCC  
 TGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCGTCGAGG  
 ^ ^  
 3332 SACI, 3346 HIND3,  
 SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly  
 3362 TCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCGCCCTTCTGGC  
 AGTTGAAGGCCGTAATGCCCGCTGTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG  
 CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluPro  
 3422 TGCCCCCCCCGACTCCGACGCTGAGTCTATTCTCCATGCCCCCCTGGAGGGGGAGCCT  
 ACGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA  
 ^  
 3437 EAM11051,  
 GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu  
 3482 GGGGATCCGGATCTTAGCGACGGGTGATGGTCAACGGTCAGTAGTGAGGCCAACCGGGAG  
 CCCCTAGGCCTAGAATCGCTGCCAGTACCAGTTGCCAGTCATCACTCCGGTTGCGCCTC  
 ^ ^ ^  
 3484 BAMHI, 3485 BSAB1, 3487 BSPE1,  
 AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla  
 3542 GATGTCGTGTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTACCCCCGTGCGCC  
 CTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCGTGAGCAGTGGGGCACGCGG

## FIGURE 17 - Page 7

3589 DRA3, 3600 SAC2,

AlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHisHisAsn  
 3602 GCGGAAGAACAGAACTGCCCATCAATGCACTAAGCAACTCGTTGCTACGTACCACAAT  
 CGCCTTCTTGTCTTTGACGGGTAGTTACGTGATTGTTGAGCAACGATGCAGTGGTGTTA  
 ^

3611 ALWN1, 3655 PFLM1,

LeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThrPheAsp  
 3662 TTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAAGAAAGTCACATTTGAC  
 AACCACATAAGGTGGTGGAGTGCCTCACGAACGGTTTCCGTCTTCTTTTCAGTGTAACCTG  
 ^

3681 DRA3,

ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla  
 3722 AGACTGCAAGTTCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCAGCGGCG  
 TCTGACGTTCAAGACCTGTCTGTAATGGTCTGCATGAGTTCCTCCAATTTTCGTCGCCCG

SerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrProProHis  
 3782 TCAAAAGTGAAGGCTAACTTGCTATCCGTAGAGGAAGCTTGACGCTGACGCCCCACAC  
 AGTTTTCACTTCCGATTGAACGATAGGCATCTCCTTCCAACGTCGGACTGCGGGGGTGTG  
 ^

3816 HIND3,

SerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArgLysAla  
 3842 TCAGCCAAATCCAAGTTTGGTTATGGGGCAAAGACGTCCGTTGCCATGCCAGAAAGGCC  
 AGTCGGTTTAGGTTCAAACCAATACCCCGTTTCTGCAGGCAACGGTACGGTCTTTCCGG  
 ^

3875 AAT2, 3890 BGLI,

ValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrProIleAsp  
 3902 GTAACCCACATCAACTCCGTGTGGAAAGACCTTCTGGAAGACAATGTAACCAATAGAC  
 CATTGGGTGTAGTTGAGGCACACCTTTCTGGAAGACCTTCTGTTACATTGTGGTTATCTG

ThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGlyArgLys  
 3962 ACTACCATCATGGCTAAGAACGAGGTTTTCTGCGTTTCAGCCTGAGAAGGGGGTTCGTAAG  
 TGATGGTAGTACCGATTCTTGTCCAAAAGACGCAAGTCGGACTCTTCCCCCAGCATTC

ProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMetAlaLeu  
 4022 CCAGCTCGTCTCATCGTGTTCCTCGATCTGGGCGTGCGCGTGTGCGAAAAGATGGCTTTG  
 GGTGCGAGCAGAGTAGCACAAGGGGCTAGACCCGCACGCGCACACGCTTTTCTACCGAAAC

TyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPheGlnTyr  
 4082 TACGACGTGGTTACAAAGCTCCCTTGGCCGTGATGGGAAGCTCCTACGGATTCCAATAC  
 ATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCCTTCGAGGATGCCTAAGGTTATG

SerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThrProMet  
 4142 TCACCAGGACAGCGGGTTGAATTCCTCGTGCAAGCGTGGAAGTCCAAGAAAACCCCAATG  
 AGTGGTCTGTGCCCCAACTTAAGGAGCACGTTGCGACCTTCAGGTTCTTTTGGGGTTAC  
 ^

4160 ECORI,

GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr  
 4202 GGGTTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATCCGTACG  
 CCCAAGAGCATACTATGGGCGACGAAACTGAGGTGTCAGTGACTCTCGCTGTAGGCATGC  
 ^

## FIGURE 17 - Page 8

4229 DRD1, 4236 ALWN1,  
 GluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIleLysSer  
 4262 GAGGAGGCAATCTACCAATGTTGTGACCTCGACCCCCAAGCCCGGTGGCCATCAAGTCC  
 CTCCTCCGTTAGATGGTTACAACACTGGAGCTGGGGGTTCTGGGCGCACCCGGTAGTTCAGG  
 4301 BGLI, 4308 BALI,  
 LeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsnCysGly  
 4322 CTCACCGAGAGGCTTTATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAGAACTGCGGC  
 GAGTGGCTCTCCGAAATACAACCCCGGGAGAATGGTTAAGTTCCCCCTCTTGACGCCG  
 4345 APAI,  
 TyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys  
 4382 TATCGCAGGTGCCGCGCAGCGCGTACTGACAACCTAGCTGTGGTAACACCCTCACTTGC  
 ATAGCGTCCACGGCGCGCTCGCCGCATGACTGTTGATCGACACCATTGTGGGAGTGAACG  
 TyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMetLeuVal  
 4442 TACATCAAGGCCCGGGCAGCCTGTCTGAGCCGCAGGGCTCCAGGACTGCACCATGCTCGTG  
 ATGTAGTTCGGGGCCCGTCGGACAGCTCGGCGTCCCCGAGGTCTGACGTGGTACGAGCAC  
 4452 SMAI XMAI,  
 CysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAlaAlaSer  
 4502 TGTGGCGACGACTTAGTCGTTATCTGTGAAAGCGCGGGGGTCCAGGAGGACGCGGCGAGC  
 ACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCCAGGTCTCTCTGCGCCGCTCG  
 4508 DRD1, 4511 TTH3I,  
 LeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspProProGln  
 4562 CTGAGAGCCTTCACGGAGGCTATGACCAGGTACTCCGCCCCCTGGGGACCCCCACAA  
 GACTCTCGGAAGTGCCTCCGATACTGGTCCATGAGGCGGGGGGACCCCTGGGGGGTGTT  
 ProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAlaHisAsp  
 4622 CCAGAATACGACTTGGAGCTCATAACATCATGCTCCTCCAACGTGTGAGTGGCCACGAC  
 GGTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTTGCACAGTCAGCGGTGCTG  
 4637 SACI,  
 GlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAlaArgAla  
 4682 GCGGCTGGAAAGAGGGTCTACTACCTCACCCGTGACCCTACAACCCCTCGCGAGAGCT  
 CCGCGACCTTTCTCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGAGCGCTCTCGA  
 4731 NRUI,  
 AlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIleMetPhe  
 4742 GCGTGGGAGACAGCAAGACACACTCCAGTCAATTCTGGCTAGGCAACATAATCATGTTT  
 CGCACCTCTGTCTGTTCTGTGTGAGGTGAGTTAAGGACCGATCCGTTGTATTAGTACAAA  
 AlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeuIleAla  
 4802 GCCCCCACTGTGGCGAGGATGATACTGATGACCCATTCTTTAGCGTCCTTATAGCC  
 CGGGGGTGTGACACCCGCTCCTACTATGACTACTGGGTAAAGAAATCGCAGGAATATCGG  
 4806 PFLM1, 4807 DRA3,  
 ArgAspGlnLeuGluGlnAlaLeuAspCysGluIleTyrGlyAlaCysTyrSerIleGlu

## FIGURE 17 - Page 9

4862 AGGGACCAGCTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCCATAGAA  
TCCCTGGTCGAACTTGTCCGGGAGCTAACGCTCTAGATGCCCCGACGATGAGGTATCTT  
4893 BGL2,  
ProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSerLeuHis  
4922 CCACTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCACTCCAC  
GGTGACCTAGATGGAGGTTAGTAAGTTTCTGAGGTACCGGAGTCGCGTAAAGTGAGGTG  
4954 NCOI,  
SerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGlyValPro  
4982 AGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGCATGCCTCAGAAAAC TTGGGGTACCG  
TCAATGAGAGGTCCACTTTAGTTATCCCACCGGCGTACGGAGTCTTTTGAACCCCATGGC  
5015 SPHI, 5035 KPNI,  
ProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAlaArgGly  
5042 CCCTTGGCAGCTTGGAGACACCGGGCCCGAGCGTCCGCGCTAGGCTTCTGGCCAGAGGA  
GGGAACGCTCGAACCTCTGTGGCCCGGCCTCGCAGGCGCGATCCGAAGACCGGTCTCCT  
5064 APAI, 5091 BALI,  
GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys  
5102 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAGCTCAAA  
CCGTCCCGACGGTATACACCGTTTCATGGAGAAGTTGACCCGTCATTCTTGTTCGAGTTT  
5113 NDEI,  
LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr  
5162 CTCACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTACGGCTGGCTAC  
GAGTGAGGTTATCGCCGGCGACCGGTTCGACCTGAACAGGCCGACCAAGTGCCGACCGATG  
5174 NOTI, 5175 EAGI XMA3, 5182 BALI, 5186 PVU2,  
SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys  
5222 AGCGGGGGAGACATTTATCACAGCGTGTCTCATGCCCGGCCCGCTGGATCTGGTTTTGC  
TCGCCCCCTCTGTAAATAGTGTGCGACAGAGTACGGGCCGGGGCGACCTAGACCAAACG  
5240 DRA3,  
LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgMetSerThrAsn  
5282 CTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCAACCGAATGAGCACGAAT  
GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTGGCTTACTCGTGCTTA  
5295 PSTI,  
ProLysProGlnArgLysThrLysArgAsnThrAsnArgArgProGlnAspValLysPhe  
5342 CCTAAACCTCAAAGAAAGACCAAACGTAACACCAACCGCGGCCGCGCAGGACGTCAAGTTC  
GGATTTGGAGTTTCTTTCTGGTTTGCATTGTGGTTGGCCGCCGGCGTCTCGAGTTCAAG  
5380 NOTI, 5381 EAGI XMA3, 5390 AAT2, 5401 SMAI XMAI,  
ProGlyGlyGlyGlnIleValGlyGlyValTyrLeuLeuProArgArgGlyProArgLeu  
5402 CCGGGTGGCGGTCAGATCGTTGGTGGAGTTTACTTGTGGCGCGCAGGGGCCCTAGATTG  
GGCCACCGCCAGTCTAGCAACCACCTCAAATGAACAACGGCGGTCCCCGGGATCTAAC

**FIGURE 17 - Page 10**

5449 APAI,

GlyValArgAlaThrArgLysThrSerGluArgSerGlnProArgGlyArgArgGlnPro  
5462 GGTGTGCGCGCGACGAGAAAGACTTCCGAGCGGTGCGAACCTCGAGGTAGACGTCAGCCT  
CCACACGCGCGCTGCTCTTTCTGAAGGCTCGCCAGCGTTGGAGCTCCATCTGCAGTCGGA  
5467 BSSH2, 5478 XMNI, 5502 XHOI, 5511 AAT2,

IleProLysAlaArgArgProGluGlyArgThrTrpAlaGlnProGlyTyrProTrpPro  
5522 ATCCCAAGGCTCGTCGGCCCGAGGGCAGGACCTGGGCTCAGCCCGGGTACCCTTGGCCC  
TAGGGGTTCCGAGCAGCCGGGCTCCCGTCTGGACCCGAGTCGGGCCCATGGGAACCGGG  
5548 ALWN1, 5558 ESP1, 5564 SMAI XMAI, 5568 KPNI,

LeuTyrGlyAsnGluGlyCysGlyTrpAlaGlyTrpLeuLeuSerProArgGlySerArg  
5582 CTCTATGGCAATGAGGGCTGCGGGTGGGCGGGATGGCTCCTGTCTCCCCGTGGCTCTCGG  
GAGATACCGTTACTCCCGACGCCCACCCGCCCTACCGAGGACAGAGGGGCACCGAGAGCC

ProSerTrpGlyProThrAspProArgArgArgSerArgAsnLeuGlyLysOC AM  
5642 CCTAGCTGGGGCCCCACAGACCCCGGCGTAGGTGCGCAATTTGGGTAAGTAATAGTCG  
GGATCGACCCCGGGGTGTCTGGGGGCCGCATCCAGCGCGTTAAACCCATTATTATCAGC  
5650 APAI, 5698 SALI,

5702 AC  
TG

## FIGURE 18 - Page 1

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn  
 2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC  
 TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG  
 ^ ^ ^  
 1 HIND3, 24 NDEI, 52 SCAI,  
 ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp  
 62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT  
 GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCCTAGCTA  
 ^  
 116 CLAI,  
 ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr  
 122 CCTAACATCAGGACCGGGGTGAGAACAATTACCACTGGCAGCCCCATCACGTACTCCACC  
 GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGCATGAGGTGG  
 TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys  
 182 TACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT  
 ATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGCAATACTGTATTATTAAACA  
 AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln  
 242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA  
 CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAAGTGGTT  
 AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal  
 302 GCAGAGACTGCGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC  
 CGTCTCTGACGCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCGAGGCAG  
 ^  
 303 ALWN1,  
 ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe  
 362 ACTGTGCCCCATCCCAACATCGAGGAGTTGCTCTGTCCACCACCGGAGAGATCCCTTTT  
 TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA  
 TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis  
 422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTCTGTCAT  
 ATGCCGTTCCGATAGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA  
 SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal  
 482 TCAAAGAAGAAGTGCGACGAAGTCCCGCAAAGCTGGTCGCATTGGGCATCAATGCCGTG  
 AGTTTCTTCTTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTACGGCAC  
 AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal  
 542 GCCTACTACCGCGGTCTTGACGTGTCCGTCATCCCGACCAGCGGCGATGTTGTGTCGTG  
 CGGATGATGGCGCCAGAACTGCACAGGCAGTAGGGCTGGTCGCCGCTACAACAGCAGCAC  
 ^ ^  
 550 SAC2, 560 DRD1,  
 AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn  
 602 GCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGACTGCAAT  
 CGTTGGCTACGGGAGTACTGGCCGATATGCCGCTGAAGCTGAGCCACTATCTGACGTTA  
 ^

## FIGURE 18 - Page 2

ThrCysValThrGlnThrValAspPh SerLeuAspProThrPheThrIleGluThrIle  
 662 ACGTGTGTCACCCAGACAGTCGATTTCAGCCTTGACCCTACCTTACCATTGAGACAATC  
 TGCACACAGTGGGTCTGTCTAGCTAAAGTCGGAACGGGATGGAAGTGGTAACTCTGTTAG

ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys  
 722 ACGTCCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGGGGGAAG  
 TGCAGGGGGTCTACGACAGAGGGCGTGAGTTGCAGCCCCGCTGACCCTCCCCCTTC

ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer  
 782 CCAGGCATCTACAGATTTGTGGCACCAGGGGAGCGCCCTCCGGCATGTTTCGACTCGTCC  
 GGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGAGGCCGTACAAGCTGAGCAGG

816 BGLI, 833 DRD1,

ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr  
 842 GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCGCCGAGACT  
 CAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAGTGCGGGCGGCTCTGA

881 SACI,

ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu  
 902 ACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGACCATCTT  
 TGTCATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCCTGGTAGAA

931 SMAI XMAI,

GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln  
 962 GAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCACTTTCTATCCCAG  
 CTTAAACCCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC

985 STUI,

ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla  
 1022 ACAAGCAGAGTGGGGAGAACCTTCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT  
 TGTTTCGTCTCACCCTCTTGAAGGAATGGACCATCGCATGGTTCGGTGGCACACGCGA

1069 DRA3,

ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys  
 1082 AGGGCTCAAGCCCCCTCCCCATCGTGGGACCAGATGTGGAAGTGTGATTGCGCTCAAG  
 TCCCGAGTTCGGGGAGGGGGTAGCACCTGGTCTACACCTTACAACTAAGCGGAGTTC

ProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsnGluIle  
 1142 CCCACCCTCCATGGGCCAACCCCCTGCTATACAGACTGGGCGCTGTTGAGAATGAAATC  
 GGGTGGGAGGTACCGGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTACTTTAG

1150 NCOI,

ThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeuGluVal  
 1202 ACCCTGACGCACCCAGTCACCAATACATCATGACATGCATGTGCGCCGACCTGGAGGTC  
 TGGGACTGCGTGGGTGAGTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGACCTCCAG

1230 BSPH1, 1234 DRD1, 1237 AVA3, 1245 EAG1 XMA3, 1250 DRD1,

ValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyrCysLeu  
 1262 GTCACGAGCACCTGGGTGCTCGTTGGCGGCGTCCTGGCTGCTTTGGCCGCGTATTGCGCTG

## FIGURE 18 - Page 3

CAGTGCTCGTGGACCCACGAGCAACCGCCGAGGACCGACGAAACCGGCGCATAACGGAC  
 SerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAlaIleIle  
 1322 TCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCGTCTTGTCCGGAAGCCGGCAATCATA  
 AGTTGTCCGACGCACCAGTATCACCCGTCCAGCAGAACAGGCCCTTCGGCCGTTAGTAT  
 1369 NAEI,  
 ProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGlnHisLeu  
 1382 CCTGACAGGGAAGTCTCTACCGAGAGTTCGATGAGATGGAAGAGTGCTCTCAGCACTTA  
 GGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCAGAGAGTCGTGAAT  
 1385 DRD1,  
 ProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeuGlyLeu  
 1442 CCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAGCAGAAGGCCCTCGGCCCTC  
 GGCATGTAGCTCGTTCCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCCGGGAGCCGGAG  
 LeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsnTrpGln  
 1502 CTGCAGACCGCGTCCCGTCAGGCAGAGTTATCGCCCCTGCTGTCCAGACCACTGGCAA  
 GACGTCTGGCGCAGGGCAGTCCGTCTCCAATAGCGGGGACGACAGGTCTGGTTGACCGTT  
 1502 PSTI, 1507 TTH3I,  
 LysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGlnTyrLeu  
 1562 AAACCTCGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAATACTTG  
 TTTGAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCCTATGTTATGAAC  
 1565 XHOI, 1586 NDEI,  
 AlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPheThrAla  
 1622 GCGGGCTTGTCAACGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTTACAGCT  
 CGCCCCAACAGTTGCGACGGACCATTTGGGGCGGTAACGAAGTAACTACCGAAAATGTCTGA  
 1643 BSTE2, 1677 ALWN1 PVU2,  
 AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp  
 1682 GCTGTCAACAGCCCACTAACCCTAGCCAAACCCTCCTCTTCAACATATTGGGGGGGTGG  
 CGACAGTGGTCGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC  
 ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla  
 1742 GTGGCTGCCAGCTCGCCGCCCGGGTGGCGCTACTGCCTTGTGGGCGCTGGCTTAGCT  
 CACCGACGGGTCGAGCGGGCGGGGCCACGGCGATGACGGAAACACCCGCGACCGAATCGA  
 1794 ESP1,  
 GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr  
 1802 GGCGCCGCCATCGGCAGTGTGGACTGGGGAAGGTCCTCATAGACATCCTTGACGGGTAT  
 CCGCGCGGCTAGCCGTCACAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCCATTA  
 1802 KAS1 NARI,  
 GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer  
 1862 GGCGCGGGCGTGGCGGGAGCTCTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCTCC  
 CCGCGCCCGACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG  
 1878 SACI, 1899 BSPH1,



## FIGURE 18 - Page 4

ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly  
 1922 ACGGAGGACCTGGTCAATCTACTGCCCCGCCATCCTCTCGCCCGGAGCCCTCGTAGTCGGC  
 TGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCATCAGCCG  
 ^  
 1928 TTH3I,  
 ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp  
 1982 GTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCGGGGAGGGGGCAGTGCAGTGG  
 CACCAGACACGTCGTTATGACGCGGCCGTGCAACCGGGGCCGCTCCCCCGTCACGTCACC  
 ^  
 2004 NAEI, 2017 SMAI XMAI,  
 MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal  
 2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTTCCCCACGCACTACGTCG  
 TACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGGTGCGTGATGCAC  
 ^  
 2067 SMAI XMAI, 2093 DRA3,  
 ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln  
 2102 CCGGAGAGCGATGCAGCTGCCCGCGTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG  
 GGCTCTCGCTACGTGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACATTGGGTG  
 ^  
 2115 PVU2, 2159 ALWN1,  
 LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer  
 2162 CTCCTGAGGCGACTGCACCACTGGATAAGCTCGGAGTGTAACCACTCCATGCTCCGGTTCC  
 GAGGACTCCGCTGACGTGGTCACCTATTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG  
 ^  
 2164 MST2, 2220 ECON1,  
 TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu  
 2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTAAAGACCTGGCTA  
 ACCGATTCCCTGTAGACCCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGGACCGAT  
 LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr  
 2282 AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCTTTGTGTCTGCCAGCGCGGGTAT  
 TTTGATTGAGTACGGTGTGCGAGGACCTAGGGGAAACACAGGACGGTCGCGCCCAT  
 ^  
 2285 ESP1, 2300 PVU2, 2310 BAMHI,  
 LysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAlaGluIle  
 2342 AAGGGGGTCTGGCGAGGGGACGGCATATGCACACTCGTGGCACTGTGGAGCTGAGATC  
 TTCCCCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG  
 ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet  
 2402 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCTAGGACCTGCAGGAACATG  
 TGACCTGTACAGTTTTTGCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCTTGTAC  
 ^  
 2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,  
 TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla  
 2462 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCTGTACCCCCCTTCTGCG  
 ACCTCACCTGGAAGGGTAATTACGGATGTGGTGGCCGGGGACATGGGGGGAAGGACGC  
 ^

## FIGURE 18 - Page 5

ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln  
 2522 CCGAACTACACGTTCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATAAGGCAG  
 GGCTTGATGTGCAAGCGCGATACCTCCCACAGACGTCTCCTTATGCACCTCTATTCCGTC  
 2553 PSTI,  
 ValGlyAspPheHisTyrValThrGlyMetThrThrAspAsnLeuLysCysProCysGln  
 2582 GTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCGTGCCAG  
 CACCCCCTGAAGGTGATGCACTGCCATACTGATGACTGTTAGAATTTACGGGCACGGTC  
 2594 DRA3,  
 ValProSerProGluPhePheThrGluLeuAspGlyValArgLeuHisArgPheAlaPro  
 2642 GTCCCATCGCCCGAATTTTTCACAGAATTGGACGGGGTGCGCCTACATAGGTTTGCGCC  
 CAGGGTAGCGGGCTTAAAAAGTGTCTTAACCTGCCCCACGCGGATGTATCCAAACGCGGG  
 ProCysLysProLeuLeuArgGluGluValSerPheArgValGlyLeuHisGluTyrPro  
 2702 CCCTGCAAGCCCTTGCTGCGGGAGGAGGTATCATTCAGAGTAGGACTCCACGAATACCCG  
 GGGACGTTGCGGAACGACGCCCTCTCCATAGTAAGTCTCATCCTGAGGTGCTTATGGGC  
 2757 HGIE2,  
 ValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSerMetLeu  
 2762 GTAGGGTCGCAATTACCTTGCGAGCCGAACCGGACGTGGCCGTGTTGACGTCCATGCTC  
 CATCCACGCGTTAATGGAACGCTCGGGCTTGGCCTGCACCGGCACAACGTCAGGTACGAG  
 2809 AAT2,  
 ThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGlySerPro  
 2822 ACTGATCCCTCCCATATAACAGCAGAGCGCGCCGGCGAAGGTTGGCGAGGGGATCACCC  
 TGA TAGGGAGGGTATATTGTCGTCTCCGCCGGCCGCTTCCAACCGCTCCCCTAGTGGG  
 2850 EAG1 XMA3,  
 ProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAlaThrCys  
 2882 CCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCAACTGC  
 GGGAGACACCGGTCGAGGAGCCGATCGGTCGATAGGCGAGGTAGAGAGTTCCGTTGAACG  
 2889 BALI, 2903 NHEI,  
 ThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuLeuTrpArgGln  
 2942 ACCGCTAACCATGACTCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAG  
 TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGTTGGAGGATACCTCCGTC  
 2966 ESPI, 2969 SACI,  
 GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer  
 3002 GAGATGGGCGGCAACATCACCAGGGTTGAGTCAGAAAACAAAGTGGTGATTCTGGACTCC  
 CTCTACCCGCCGTTGTAGTGGTCCCAACTCAGTCTTTTGTTCACCACTAAGACCTGAGG  
 PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu  
 3062 TTCGATCCGCTTGTGGCGGAGGAGGACGAGCGGGAGATCTCCGTACCCGCAGAAATCCTG  
 AAGCTAGGCGAACACCGCCTCCTCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC  
 3096 BGL2,  
 ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro

## FIGURE 18 - Page 6

3122 CGGAAGTCTCGGAGATTGCCCCAGGCCCTGCCCCGTTTGGGCGCGGCCGGACTATAACCCC  
 GCCTTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGGCCTGATATTGGGG  
 3143 ALWN1, 3164 EAG1 XMA3,  
 ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro  
 3182 CCGCTAGTGGAGACGTGGAAAAAGCCCGACTACGAACCACCTGTGGTCCATGGCTGCCCG  
 GCGCATCACCTCTGCACCTTTTCGGGGCTGATGCTTGGTGGACACCAGGTACCAGCGGGC  
 3217 HGIE2, 3229 NCOI,  
 LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu  
 3242 CTTCCACCTCCAAAGTCCCCTCCTGTGCCTCCGCCCTCGGAAGAAGCGGACGGTGGTCCTC  
 GAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCACCAGGAG  
 ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSer  
 3302 ACTGAATCAACCCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGCAGCTCC  
 TGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCGTCGAGG  
 3332 SACI, 3346 HIND3,  
 SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly  
 3362 TCAACTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCCCCCCTTCTGGC  
 AGTTGAAGGCCGTAATCCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG  
 CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluPro  
 3422 TGCCCCCGGACTCCGACGCTGAGTCCTATTCTCCATGCCCCCCTGGAGGGGGAGCCT  
 ACGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA  
 3437 EAM11051,  
 GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu  
 3482 GGGGATCCGGATCTTAGCGACGGGTCATGGTCAACGGTCAGTAGTGAGCCAACGCGGAG  
 CCCCTAGGCCTAGAATCGCTGCCAGTACCAGTTGCCAGTCATCACTCCGGTTGCGCCTC  
 3484 BAMHI, 3485 BSAB1, 3487 BSPE1,  
 AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla  
 3542 GATGTCGTGTGCTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCACCCCGTGCGCC  
 CTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCGTGAGCAGTGGGGCACGCGG  
 3589 DRA3, 3600 SAC2,  
 AlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHisHisAsn  
 3602 GCGGAAGAACAGAACTGCCCATCAATGCCTAAGCAACTCGTTGCTACGTACCCACAAT  
 CGCCTTCTTGTCTTTGACGGGTAGTTACGTGATTGCTTGGCAACGATGCAGTGGTGTTA  
 3611 ALWN1, 3655 PFLM1,  
 LeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThrPheAsp  
 3662 TTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAAGAAAGTCACATTTGAC  
 AACCACATAAGGTGGTGGAGTGCGTCACGAACGGTTTCCGTCTTCTTTCACTGTAAACTG  
 3681 DRA3,  
 ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla  
 3722 AGACTGCAAGTTCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCAGCGGCG

## FIGURE 18 - Page 7

TCTGACGTTCAAGACCTGTCGGTAATGGTCCTGCATGAGTTCCTCCAATTTTCGTCGCCGC

3782 SerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrProProHis  
TCAAAAGTGAAGGCTAACTTGCTATCCGTAGAGGAAGCTTGCAGCCTGACGCCCCACAC  
AGTTTTCACTTCCGATTGAACGATAGGCATCTCCTTCGAACGTGCGACTGCGGGGGTGTG

3816 HIND3,

3842 SerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArgLysAla  
TCAGCCAAATCCAAGTTTGGTTATGGGGCAAAGACGTCCTGTCATGCCAGAAAGGCC  
AGTCGGTTTAGGTTCAAACCAATACCCCGTTTTCTGCAGGCAACGGTACGGTCTTTCCGG

3875 AAT2, 3890 BGLI,

3902 ValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrProIleAsp  
GTAACCCACATCAACTCCGTGTGGAAGACCTTCTGGAAGACAATGTAACACCAATAGAC  
CATTGGGTGTAGTTGAGGCACACCTTTCTGGAAGACCTTCTGTTACATTGTGGTTATCTG

3962 ThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGlyArgLys  
ACTACCATCATGGCTAAGAACGAGGTTTTCTGCGTTCAGCCTGAGAAGGGGGTTCGTAAG  
TGATGGTAGTACCGATTCTTGCTCCAAAAGACGCAAGTCGGACTCTTCCCCCAGCATTCT

4022 ProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMetAlaLeu  
CCAGCTCGTCTCATCGTGTTCCTCGATCTGGGCGTGCAGCGTGTGCGAAAAGATGGCTTTG  
GGTCGAGCAGAGTAGCACAAGGGGCTAGACCCGCACGCGCACACGCTTTTCTACCGAAAC

4082 TyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPheGlnTyr  
TACGACGTGGTTACAAAGCTCCCTTGGCCGTGATGGGAAGCTCCTACGGATTCCAATAC  
ATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCCTTCGAGGATGCCTAAGGTTATG

4142 SerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThrProMet  
TCACCAGGACAGCGGGTTGAATTCCTCGTGCAAGCGTGGAAGTCCAAGAAAACCCCAATG  
AGTGGTCTGTGCCCCAACTTAAGGAGCACGTTTCGCACCTTCAGGTTCTTTTGGGGTTAC

4160 ECORI,

4202 GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr  
GGGTTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATCCGTACG  
CCCAAGAGCATACTATGGGCGACGAACTGAGGTGTCTAGTACTCTCGCTGTAGGCATGC

4229 DRD1, 4236 ALWN1,

4262 GluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIleLysSer  
GAGGAGGCAATCTACCAATGTTGTGACCTCGACCCCAAGCCCGCTGGCCATCAAGTCC  
CTCCTCCGTTAGATGGTTACAACACTGGAGCTGGGGGTTTCGGGCGCACCGGTAGTTCAGG

4301 BGLI, 4308 BALI,

4322 LeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsnCysGly  
CTCACCGAGAGGCTTTATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAGAACTGCGGC  
GAGTGGCTCTCCGAAATACAACCCCGGGGAGAATGGTTAAGTTCCCCCTCTTGACGCCG

4345 APAI,

4382 TyrArgArgCysArgAlaS rGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys  
TATCGAGGTGCCGCGGAGCGGCTACTGACAAGTCTGTGGTAACACCCCTCACTTGC  
ATAGCGTCCACGGCGCGCTCGCCGCATGACTGTTGATCGACACCATTGTGGGAGTGAACG

## FIGURE 18 - Page 8

TyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMetLeuVal  
 4442 TACATCAAGGCCCGGGCAGCCTGTGCGAGCCGAGGGCTCCAGGACTGCACCATGCTCGTG  
 ATGTAGTTCCGGGCCCGTCCGACAGCTCGGCGTCCCGAGGTCCTGACGTGGTACGAGCAC  
 ^  
 4452 SMAI XMAI,  
 CysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAlaAlaSer  
 4502 TGTGGCGACGACTTAGTCGTTATCTGTGAAAGCGCGGGGGTCCAGGAGGACGCGGCGAGC  
 ACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCCAGGTCCTCCTGCGCCGCTCG  
 ^ ^  
 4508 DRD1, 4511 TTH3I,  
 LeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspProProGln  
 4562 CTGAGAGCCTTCACGGAGGCTATGACCAGGTACTCCGCCCCCCTGGGGACCCCCACAA  
 GACTCTCGGAAGTGCTCCGATACTGGTCCATGAGGCGGGGGGACCCCTGGGGGGTGTT  
 ProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAlaHisAsp  
 4622 CCAGAATACGACTTGGAGCTCATAACATCATGCTCCTCCAACGTGTCAGTCGCCCCACGAC  
 GGTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTTGCACAGTCAGCGGGTGCTG  
 ^  
 4637 SACI,  
 GlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAlaArgAla  
 4682 GCGCTGGAAAGAGGGTCTACTACCTCACCCGTGACCCTACAACCCCCCTCGCGAGAGCT  
 CCGCGACCTTTCTCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGGAGCGCTCTCGA  
 ^  
 4731 NRUI,  
 AlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIleMetPhe  
 4742 GCGTGGGAGACAGCAAGACACACTCCAGTCAATTCCTGGCTAGGCAACATAATCATGTTT  
 CGCACCTCTGTCGTTCTGTGTGAGGTCAAGTAAAGACCGATCCGTTGTATTAGTACAAA  
 AlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeuIleAla  
 4802 GCCCCACACTGTGGGCGAGGATGATACTGATGACCCATTTCTTTAGCGTCCTTATAGCC  
 CGGGGGTGTTGACACCCGCTCCTACTATGACTACTGGGTAAAGAAATCGCAGGAATATCGG  
 ^ ^  
 4806 PFLM1, 4807 DRA3,  
 ArgAspGlnLeuGluGlnAlaLeuAspCysGluIleTyrGlyAlaCysTyrSerIleGlu  
 4862 AGGGACCAGCTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCCATAGAA  
 TCCTTGGTGAACCTTGTCCGGGAGCTAACGCTCTAGATGCCCCGACGATGAGGTATCTT  
 ^  
 4893 BGL2,  
 ProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSerLeuHis  
 4922 CCACTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCACTCCAC  
 GGTGACCTAGATGGAGGTTAGTAAGTTTCTGAGGTACCGGAGTCGCGTAAAAGTGAGGTG  
 ^  
 4954 NCOI,  
 SerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGlyValPro  
 4982 AGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGCATGCCTCAGAPAACTTGGGGTACCG  
 TCAATGAGAGGTCCACTTTAGTTATCCACCGGCGTACGGAGTCTTTGAACCCCATGGC  
 ^ ^  
 5015 SPHI, 5035 KPNI,

## FIGURE 18 - Page 9

ProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAlaArgGly  
 5042 CCCTTGCGAGCTTGGAGACACGGGCCCCGGAGCGTCCGCGCTAGGCTTCTGGCCAGAGGA  
 GGAACGCTCGAACCTCTGTGGCCCCGGCCTCGCAGGCGCGATCCGAAGACCGGTCTCCT  
 5064 APAI, 5091 BALI,  
 GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys  
 5102 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAGCTCAA  
 CCGTCCCAGCGGTATACACCGTTCATGGAGAAGTTGACCCGTCATTCTTGTTTCGAGTTT  
 5113 NDEI,  
 LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr  
 5162 CTACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCGGCTGGTTCACGGCTGGCTAC  
 GAGTGAGTTATCGCCGGCGACCGGTGACCTGAACAGGCCGACCAAGTCCGACCGATG  
 5174 NOTI, 5175 EAGI XMA3, 5182 BALI, 5186 PVU2,  
 SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys  
 5222 AGCGGGGGAGACATTTATCACAGCGTGTCTCATGCCCGGCCCGCTGGATCTGGTTTTGC  
 TCGCCCCCTCTGTAAATAGTGTGCGACAGAGTACGGGCCGGGGCGACCTAGACCAAACG  
 5240 DRA3,  
 LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgMetSerThrAsn  
 5282 CTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCAACCGAATGAGCACGAAT  
 GATGAGGACGAACGACGTCCCATCCGTAGATGGAGGAGGGGTGGCTTACTCGTGCTTA  
 5295 PSTI,  
 ProLysProGlnArgLysThrLysArgAsnThrAsnArgArgProGlnAspValLysPhe  
 5342 CCTAAACCTCAAAGAAAGACCAAACGTAACACCAACCGGCCGCGCAGGACGTCAAGTTC  
 GGATTTGGAGTTTCTTTCTGGTTTGCATTGTGGTTGGCCGCCGCGTCTGCAGTTCAAG  
 5380 NOTI, 5381 EAGI XMA3, 5390 AAT2, 5401 SMAI XMAI,  
 ProGlyGlyGlyGlnIleValGlyGlyValTyrLeuLeuProArgArgGlyProArgLeu  
 5402 CCGGGTGGCGGTGAGATCGTTGGTGGAGTTTACTTGTTGCCGCGCAGGGGCCCTAGATTG  
 GGCCACCGCCAGTCTAGCAACCACCTCAAATGAACAACGGCGCGTCCCCGGGATCTAAC  
 5449 APAI,  
 GlyValArgAlaThrArgLysThrSerGluArgSerGlnProArgGlyArgArgGlnPro  
 5462 GGTGTGCGCGCGACGAGAAAGACTTCCGAGCGGTGCAACCTCGAGGTAGACGTACGCCT  
 CCACACGCGCGCTGCTCTTTCTGAAGGCTCGCCAGCGTTGGAGCTCCATCTGCAGTCGGA  
 5467 BSSH2, 5478 XMNI, 5502 XHOI, 5511 AAT2,  
 IleProLysAlaArgArgProGluGlyArgThrTrpAlaGlnProGlyTyrProTrpPro  
 5522 ATCCCCAAGGCTCGTCGGCCCCGAGGGCAGGACCTGGGCTCAGCCCCGGGTACCTTGGCCC  
 TAGGGGTTCCGAGCAGCCGGGCTCCCGTCTGGACCCGAGTCGGGGCCCATGGGAACCGGG  
 5548 ALWN1, 5558 ESP1, 5564 SMAI XMAI, 5568 KPNI,  
 LeuTyrGlyAsnGluGlyCysGlyTrpAlaGlyTrpLeuLeuSerProArgGlySerArg  
 5582 CTCTATGGCAATGAGGGCTCGGGGTGGCGGGATGGCTCCTGTCTCCCGTGGCTCTCGG  
 GAGATACCGTTACTCCCGACGCCCCACCGCCCTACCGAGGACAGAGGGGCACCGAGAGCC

## FIGURE 18 - Page 10

ProSerTrpGlyProThrAspProArgArgArgSerArgAsnLeuGlyLysValIleAsp  
5642 CCTAGCTGGGGCCCCACAGACCCCGGCGTAGGTCGCGCAATTTGGGTAAGGTCATCGAT  
GGATCGACCCCGGGTGTCTGGGGGCCGATCCAGCGCGTTAAACCCATTCCAGTAGCTA  
5650 APAI, 5696 CLAI,  
ThrLeuThrCysGlyPheAlaAspLeuMetGlyTyrIleProLeuValGlyAlaProLeu  
5702 ACCCTTACGTGCGGCTTCGCCGACCTCATGGGGTACATACCGCTCGTCGGCGCCCCCTCTT  
TGGGAATGCACGCCGAAGCGGCTGGAGTACCCCATGTATGGCGAGCAGCCGCGGGGAGAA  
5724 HGIE2, 5750 KAS1 NARI, 5756 ECON1,  
GlyGlyAlaAlaArgAlaLeuAlaHisGlyValArgValLeuGluAspGlyValAsnTyr  
5762 GGAGGCGCTGCCAGGGCCCTGGCGCATGGCGTCCGGGTCTGGAAGACGGCGTGAACCTAT  
CCTCCGCGACGGTCCCGGGACCGGTACCGCAGGCCCAAGACCTTCTGCCGCACTTGATA  
5772 BSTXI, 5775 APAI,  
AlaThrGlyAsnLeuProGlyCysSerOC AM  
5822 GCAACAGGGAACCTTCCTGGTTGCTCTTAATAGTCGAC  
CGTTGTCCCTTGGAAGGACCAACGAGAATTATCAGCTG  
5854 SALI,

FIGURE 19

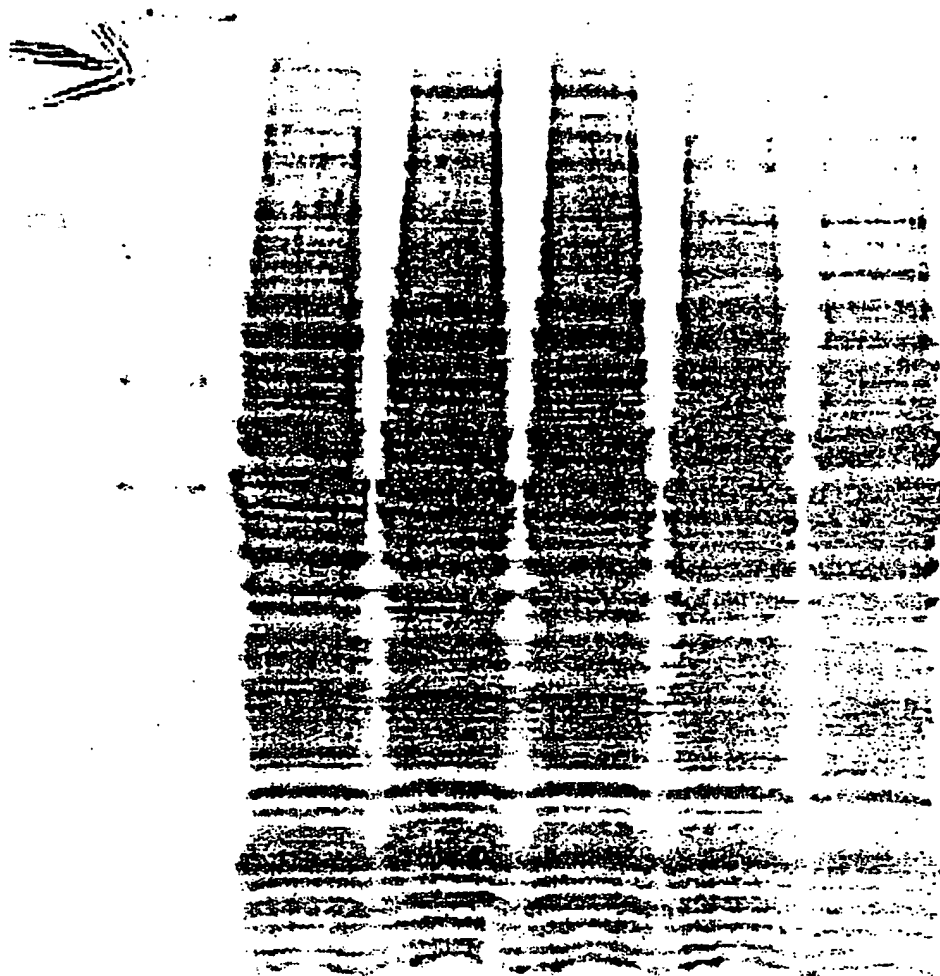




FIGURE 20 - Page 1

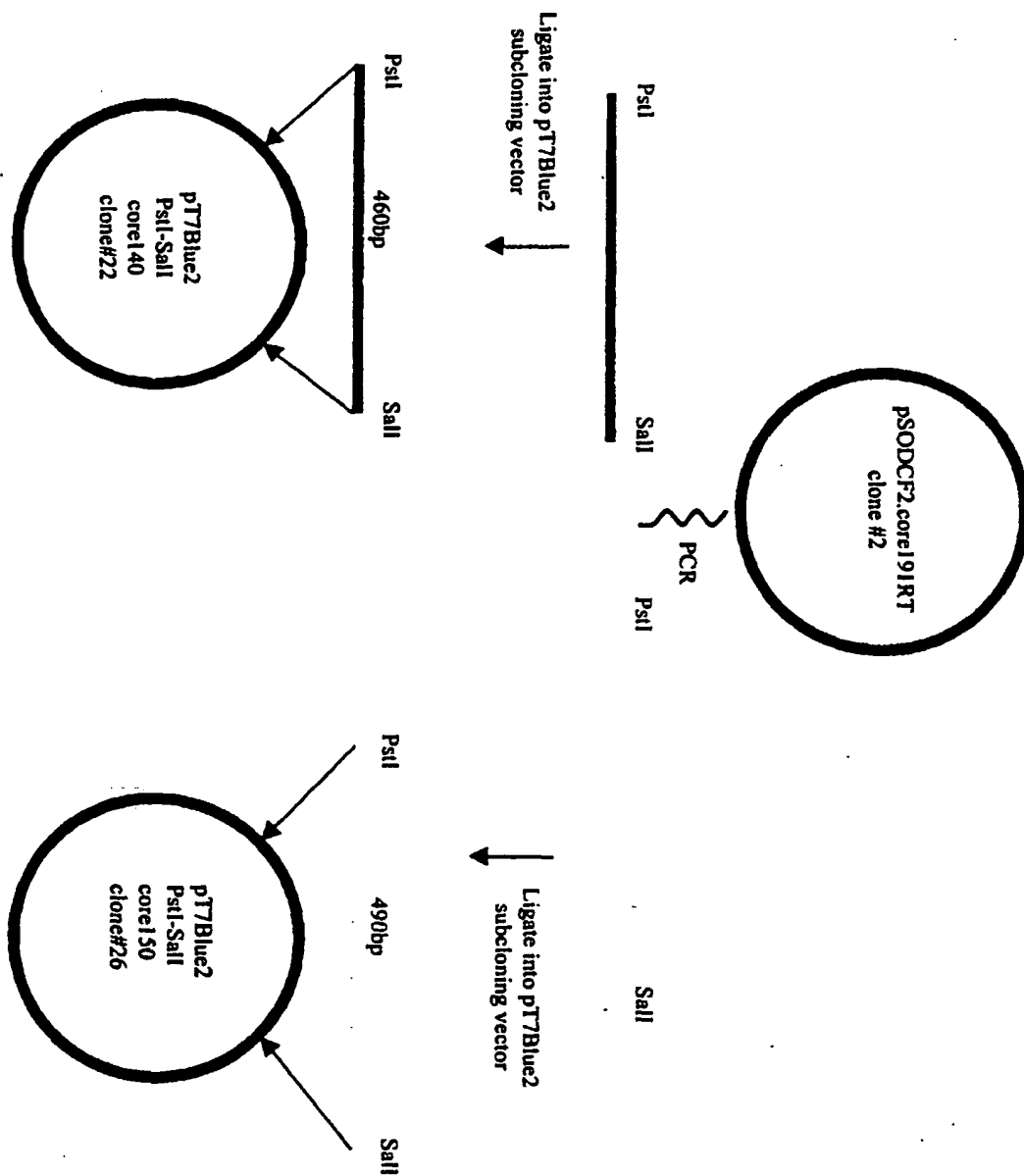
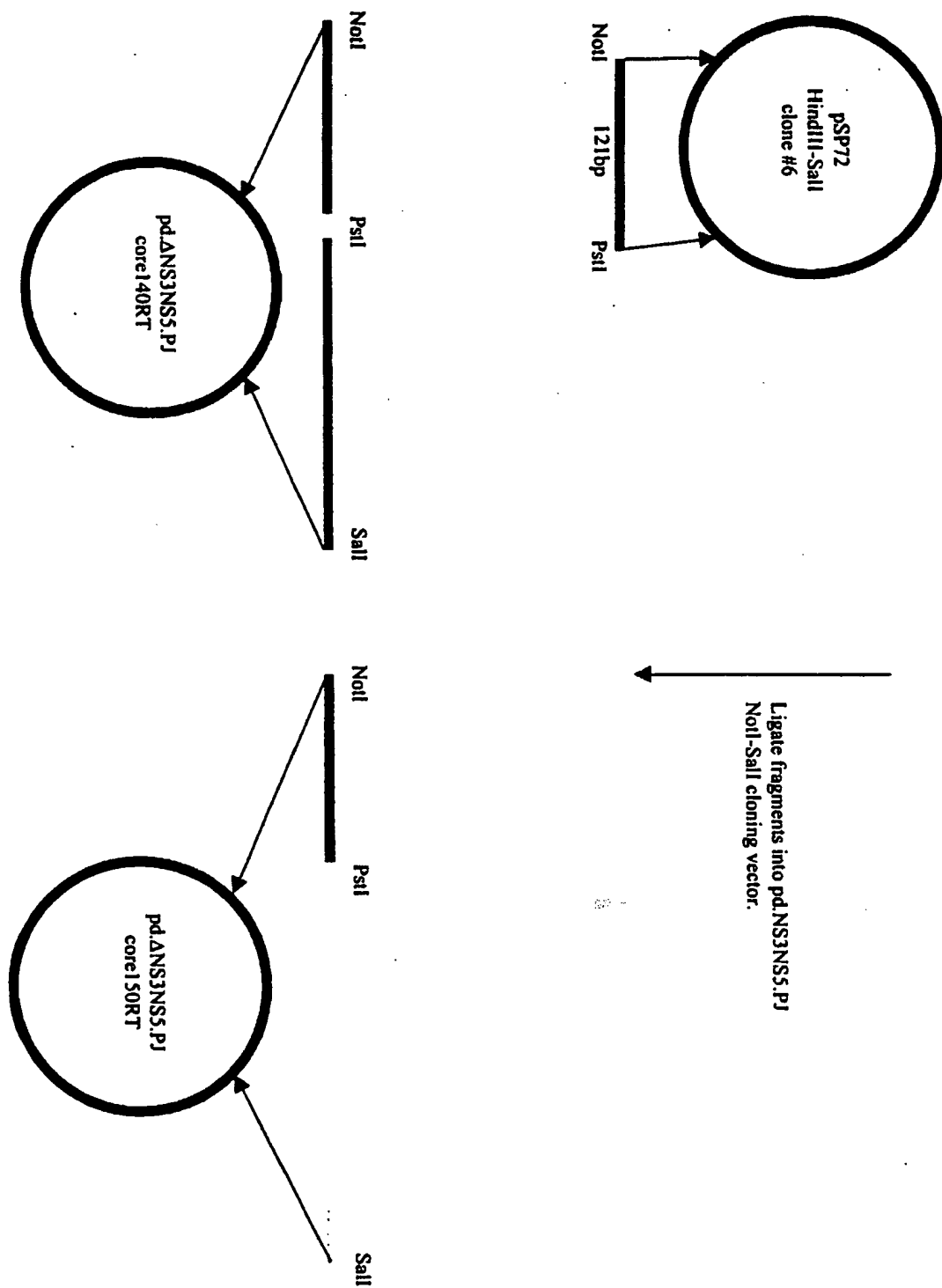


FIGURE 20 - Pa<sub>6</sub>-2<sup>1</sup>



## FIGURE 21 - Page 1

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn  
 2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC  
 TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG  
 ^ ^ ^  
 1 HIND3, 24 NDEI, 52 SCAI,

ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp  
 62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT  
 GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCCTAGCTA  
 ^  
 116 CLAI,

ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr  
 122 CCTAACATCAGGACCGGGGTGAGAACAATTACCACTGGCAGCCCCATCAGTACTCCACC  
 GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGTCATGAGGTGG

TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys  
 182 TACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT  
 ATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGGAATACTGTATTATTAAACA

AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln  
 242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCTTGACCAA  
 CTGCTCAGGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAACCTGGTT

AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal  
 302 GCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC  
 CGTCTCTGACGCCCCCGCTCTGACCAACACGAGCGGTGCGGTGGGGAGGCCCGAGGCAG  
 ^  
 303 ALWN1,

ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe  
 362 ACTGTGCCCCATCCCAACATCGAGGAGGTTGCTCTGTCCACCACCGGAGAGATCCCTTTT  
 TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA

TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis  
 422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTCTGTGCAT  
 ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA

## FIGURE 21 - Page 2

SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal  
 482 TCAAAGAAGAAGTGCGACGAACCTCGCCGCAAAGCTGGTCGCATTGGGCATCAATGCCGTG  
 AGTTTTCTTCTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTACGGCAC  
  
 AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal  
 542 GCCTACTACCGCGGTCTTGACGTGTCCGTCATCCCGACCAGCGGCATGTTGTCTCGTCGTG  
 CGGATGATGGCGCCAGAACTGCACAGGCAGTAGGGCTGGTCGCCGCTACAACAGCAGCAC  
 ^ ^  
 550 SAC2, 560 DRD1,  
  
 AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn  
 602 GCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGACTGCAAT  
 CGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTGACGTTA  
 ^  
 615 BSPH1,  
  
 ThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGluThrIle  
 662 ACGTGTGTACCCAGACAGTCGATTTACGCCTTGACCCTACCTTCACCATTGAGACAATC  
 TGCACACAGTGGGTCTGTCTAGCTAAAGTCGGAAGTGGGATGGAAGTGGTAACTCTGTTAG  
  
 ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys  
 722 ACGCTCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGGGGGAAG  
 TGCGAGGGGGTTCTACGACAGAGGGCGTGAGTTGCAGCCCCGCTCTGACCGTCCCCCTTC  
  
 ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer  
 782 CCAGGCATCTACAGATTTGTGGCACCAGGGGAGCGCCCTCCGGCATGTTGACTCGTCC  
 GGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTGAGCAGG  
 ^ ^  
 816 BGLI, 833 DRD1,  
  
 ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr  
 842 GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCCGCCGAGACT  
 CAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAAGTGGGGGGGCTCTGA  
 ^  
 881 SACI,  
  
 ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu  
 902 ACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGACCATCTT  
 TGTCAATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCTCTGGTAGAA  
 ^  
 931 SMAI XMAI,  
  
 GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln  
 962 GAATTTTGGGAGGGCGTCTTTACAGGCCCTCACTCATATAGATGCCCACTTTCTATCCAG  
 CTTAAACCCCTCCCGCAGAAATGTCGGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC  
 ^  
 985 STUI,  
  
 ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla  
 1022 ACAAAGCAGAGTGGGGAGAACCTTCCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT  
 TGTTTCGTCTACCCCTCTTGAAGGAATGGACCATCGCATGGTTCGGTGGCACACGCCGA  
 ^  
 1069 DRA3,  
  
 ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys  
 1082 AGGGCTCAAGCCCCCTCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTCGCCTCAAG

## FIGURE 21 - Page 3

TCCCGAGTTCGGGGAGGGGGTAGCACCTGGTCTACACCTTCACAACTAAGCGGAGTTC

1142 ProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsnGluIle  
 CCCACCCTCCATGGGCCAACACCCCTGCTATACAGACTGGGCGCTGTTTCTAGAAATGAAATC  
 GGGTGGGAGGTACCCGGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTACTTTAG  
 ^  
 1150 NCOI,

1202 ThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeuGluVal  
 ACCCTGACGCACCCAGTCACCAAATACATCATGACATGCATGTCGGCCGACCTGGAGGTC  
 TGGGACTGCGTGGGTGAGTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGACCTCCAG  
 ^ ^ ^ ^ ^  
 1230 BSPH1, 1234 DRD1, 1237 AVA3, 1245 EAG1 XMA3, 1250 DRD1,

1262 ValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyrCysLeu  
 GTCACGAGCACCCTGGGTGCTCGTTGGCGGCGTCTGGCTGCTTTGGCCGCGTATTGCCTG  
 CAGTGCTCGTGGACCCACGAGCAACCGCCGAGGACCGACGAAACCGGCGCATAACGGAC

1322 SerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAlaIleIle  
 TCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCTGTTGTCCGGGAAGCCGCAATCATA  
 AGTTGTCCGACGCACCAAGTATCACCCGTCCCAGCAGAACAGGCCCTTCGGCCGTTAGTAT  
 ^  
 1369 NAEI,

1382 ProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGlnHisLeu  
 CCTGACAGGGAAGTCTCTACCGAGAGTTCGATGAGATGGAAGAGTGCTCTCAGCACTTA  
 GGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCAGAGAGTCGTGAAT  
 ^  
 1385 DRD1,

1442 ProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeuGlyLeu  
 CCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAGCAGAAGGCCCTCGGCCCTC  
 GGCATGTAGCTCGTTCCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCGGGAGCCGGAG

1502 LeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsnTrpGln  
 CTGCAGACCGCTCCCGTCAGGCAGAGGTTATCGCCCTGCTGTCCAGACCAACTGGCAA  
 GACGTCTGGCGCAGGGCAGTCCGTCTCCAATAGCGGGGACGACAGGTCTGGTTGACCGTT  
 ^ ^  
 1502 PSTI, 1507 TTH3I,

1562 LysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGlnTyrLeu  
 AAACCTCGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAATACTTG  
 TTTGAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCCATGTTATGAAC  
 ^ ^  
 1565 XHOI, 1586 NDEI,

1622 AlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPheThrAla  
 GCGGGCTTGTCACGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTTACAGCT  
 CGCCCGAACAGTTGCGACGGACCATTTGGGGCGGTAACGAAGTAACCTACCGAAAATGTGCA  
 ^  
 1643 BSTE2, 1677 ALWN1 PVU2,

1682 AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp  
 GCTGTCAACAGCCCACTAACCCTAGCCAAACCTCCTCTTCAACATATTGGGGGGGTGG  
 CGACAGTGGTGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC

## FIGURE 21 - Page 4

ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla  
 1742 GTGGCTGCCCAGCTCGCCGCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT  
 CACCGACGGGTCGAGCGGCGGGGGCCACGGCGATGACGGAAACACCCGCGACCGAATCGA  
 1794 ESP1,  
 GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr  
 1802 GGCGCCGCCATCGGCAGTGTGGACTGGGGAAGGTCTCATAGACATCCTTGCAGGGTAT  
 CCGCGGCGGTAGCCGTCACAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCCAT  
 1802 KAS1 NARI,  
 GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer  
 1862 GGCGCGGGCGTGCGGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCTCC  
 CCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG  
 1878 SACI, 1899 BSPH1,  
 ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly  
 1922 ACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCGTAGTCGGC  
 TGCCTCCTGGACCACTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCATCAGCCG  
 1928 TTH3I,  
 ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp  
 1982 GTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCGGGCGAGGGGGCAGTGCAGTGG  
 CACCAGACACGTCGTTATGACGCGGCCGTGCAACCGGGCCCGCTCCCCGTCACGTACCC  
 2004 NAEI, 2017 SMAI XMAI,  
 MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal  
 2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTTCCCCACGCACTACGTG  
 TACTTGGCCGACTATCGGAAGCGGAGGCCCTTGGTACAAAGGGGGTGCGTGATGCAC  
 2067 SMAI XMAI, 2093 DRA3,  
 ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln  
 2102 CCGGAGAGCGATGCAGCTGCCCGCGTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG  
 GGCTCTCGCTACGTGACGGGCGCAGTGACGGTATGAGTCGTGCGAGTGACATTGGGTC  
 2115 PVU2, 2159 ALWN1,  
 LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer  
 2162 CTCCTGAGGCGACTGCACCACTGGATAAGCTCGGAGTGTACCACTCCATGCTCCGGTTCC  
 GAGGACTCCGCTGACGTGGTCACCTATTTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG  
 2164 MST2, 2220 ECON1,  
 TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu  
 2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACCTGGCTA  
 ACCGATTCCCTGTAGACCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGGACCGAT  
 2282 LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr  
 AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCTTTGTGTCCTGCCAGCGCGGGTAT  
 TTTGATTGAGTACGGTGTGACGGACCTAGGGGAAACACAGGACGGTTCGCGCCCAT  
 2285 ESP1, 2300 PVU2, 2310 BAMHI,

## FIGURE 21 - Page 5

LysGlyValTrpArgGlyAspGlyIleM tHisThrArgCysHisCysGlyAlaGluIle  
2342 AAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC  
TTCCCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG

ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet  
2402 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCCTAGGACCTGCAGGAACATG  
TGACCTGTACAGTTTTTGGCCCTGCTACTCTAGCAGCCAGGATCCTGGACGTCCTTGTAC  
^ ^ ^  
2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,

TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla  
2462 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCTGTACCCCCCTTCCTGCG  
ACCTCACCTGGAAGGGGTAAATTACGGATGTGGTGGCCGGGGACATGGGGGAAGGACGC  
^ ^  
2480 ASE1, 2497 APAI,

ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln  
2522 CCGAACTACACGTTTCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATAAGGCAG  
GGCTTGATGTGCAAGCGCGATACCTCCCACAGACGTCTCCTTATGCACCTCTATTCCGTC  
^  
2553 PSTI,

ValGlyAspPheHisTyrValThrGlyMetThrThrAspAsnLeuLysCysProCysGln  
2582 GTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCCGTGCCAG  
CACCCCCTGAAGGTGATGCACTGCCCATACTGATGACTGTAGAAATTTACGGGCACGGTC  
^  
2594 DRA3,

ValProSerProGluPhePheThrGluLeuAspGlyValArgLeuHisArgPheAlaPro  
2642 GTCCCATCGCCGAATTTTTTACAGAATTGGACGGGGTGGCGCTACATAGGTTTGCGCCC  
CAGGGTAGCGGGCTTAAAAAGTGTCTTAACCTGCCCCACGCGGATGTATCCAAACGCGGG

ProCysLysProLeuLeuArgGluGluValSerPheArgValGlyLeuHisGluTyrPro  
2702 CCCTGCAAGCCCTTGCTGCGGGAGGAGGTATCATTCAGAGTAGGACTCCACGAATACCCG  
GGGACGTTGCGGAACGACGCCCTCCTCCATAGTAAGTCTCATCTGAGGTGCTTATGGGC  
^  
2757 HGIE2,

ValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSerMetLeu  
2762 GTAGGGTCGCAATTACCTTGCAGCCCCGAACCGGACGTGGCCGTGTTGACGTCCATGCTC  
CATCCCAGCGTTAATGGAACGCTCGGGCTTGGCCTGCACCGGCACAACTGCAGGTACGAG  
^  
2809 AAT2,

ThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGlySerPro  
2822 ACTGATCCCTCCCATATAACAGCAGAGGCCGCGGGCGAAGGTTGGCGAGGGGATCACCC  
TGACTAGGGAGGGTATATTGTCGTCTCCGCCGGCCCGCTTCCAACCGCTCCCTAGTGGG  
^  
2850 EAG1 XMA3,

ProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAlaThrCys  
2882 CCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCAACTTGC  
GGGAGACACCGGTCGAGGAGCCGATCGGTTCGATAGGCGAGGTAGAGAGTTCCGTTGAACG  
^ ^  
2889 BALI, 2903 NHEI,

## FIGURE 21 - Page 6

ThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuLeuTrpArgGln  
 2942 ACCGCTAACCATGACTCCCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAG  
 TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGTTGGAGGATACCTCCGTC  
 ^ ^  
 2966 ESPl, 2969 SAcI,  
 GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer  
 3002 GAGATGGGCGGCAACATCACCAGGGTTGAGTCAGAAAACAAAGTGGTGATTCTGGACTCC  
 CTCTACCCGCCGTTGTAGTGGTCCCACTCAGTCTTTTGTTCACCACTAAGACCTGAGG  
 PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu  
 3062 TTCGATCCGCTTGTGGCGGAGGAGGACGAGCGGGAGATCTCCGTACCCGCAGAAATCCTG  
 AAGCTAGGCGAACACCGCCTCCTCCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC  
 ^  
 3096 BGL2,  
 ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro  
 3122 CGGAAGTCTCGGAGATTGCGCCAGGCCCTGCCCGTTTGGGCGCGGCCGGACTATAACCCC  
 GCCTTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGCTGATATTGGGG  
 ^  
 3143 ALWN1, 3164 EAG1 XMA3,  
 ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro  
 3182 CCGCTAGTGGAGACGTGAAAAAGCCCGACTACGAACCACCTGTGGTCCATGGCTGCCCCG  
 GGCGATCACCTCTGCACCTTTTTCGGGCTGATGCTTGGTGGACACCAGTACCGACGGGC  
 ^  
 3217 HGIE2, 3229 NCOI,  
 LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu  
 3242 CTTCCACCTCCAAAGTCCCCTCCTGTGCCTCCGCCCTCGGAAGAAGCGGACGGTGGTCCCTC  
 GAAGGTGGAGGTTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCACCAGGAG  
 ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSer  
 3302 ACTGAATCAACCCTATCTACTGCCTTGCCCGAGCTCGCCACCAGAAAGCTTTGGCAGCTCC  
 TGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCGTCGAGG  
 ^  
 3332 SAcI, 3346 HIND3,  
 SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly  
 3362 TCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCGCCCCTTCTGGC  
 AGTTGAAGGCCGTAATGCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG  
 CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluPro  
 3422 TGCCCCCCCCGACTCCGACGCTGAGTCCTATTCTCCATGCCCCCCTGGAGGGGGAGCCT  
 ACGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA  
 ^  
 3437 EAM11051,  
 GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu  
 3482 GGGGATCCGGATCTTAGCGACGGGTGATGGTCAACGGTCAGTAGTGAGGCCAACCGGGAG  
 CCCCTAGGCCTAGAATCGCTGCCAGTACCAGTTGCCAGTCATCACTCCGTTGCGCCTC  
 ^ ^  
 3484 BAMHI, 3485 BSAB1, 3487 BSPE1,  
 AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla  
 3542 GATGTCGTGTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCACCCCGTGCGCC  
 CTACAGCACACGACGAGTTACAGATGAGAACCTGTCCGCGTGAGCAGTGGGGCACGCGG



## FIGURE 21 - Page 7

3589 DRA3, 3600 SAC2,

3602 AlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHisHisAsn  
 GCGGAAGAACAGAACTGCCCATCAATGCACTAAGCAACTCGTTGCTACGTCACCACAAT  
 CGCCTTCTTGTCTTTGACGGGTAGTTACGTGATTCTGTTGAGCAACGATGCAGTGGTGTTA  
 ^ ^

3611 ALWN1, 3655 PFLM1,

3662 LeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThrPheAsp  
 TTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAAGAAAGTCACATTTGAC  
 AACCACATAAGGTGGTGGAGTGCCTCACGAACGGTTTCCGTCTTCTTTCAGTGTAAGTGC  
 ^

3681 DRA3,

3722 ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla  
 AGACTGCAAGTTCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCAGCGGCG  
 TCTGACGTTCAAGACCTGTCGGTAATGGTCTGCATGAGTTCCTCAATTTCTGTCGCCCGC

3782 SerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrProProHis  
 TCAAAAGTGAAGGCTAACTTGCTATCCGTAGAGGAAGCTTGACGCTGACGCCCCACAC  
 AGTTTTCACITCCGATTGAACGATAGGCATCTCCTTGAACGTCGGAAGTGCAGGCGGTGTG  
 ^

3816 HIND3,

3842 SerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArgLysAla  
 TCAGCCAAATCCAAGTTTGGTTATGGGGCAAAGACGTCCGTTGCCATGCCAGAAAGGCC  
 AGTCGGTTTAGGTTCAAACCAATACCCCGTTTTCTGCAGGCAACGGTACGGTCTTTCCGG  
 ^ ^

3875 AAT2, 3890 BGLI,

3902 ValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrProIleAsp  
 GTAACCCACATCAACTCCGTGTGGAAAGACCTTCTGGAAGACAATGTAACACCAATAGAC  
 CATTGGGTGTAGTTGAGGCACACCTTTCTGGAAGACCTTCTGTTACATTGTGGTTATCTG

3962 ThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGlyArgLys  
 ACTACCATCATGGCTAAGAACGAGTTTTCTGCGTTCAGCCTGAGAAGGGGGGTTCGTAAG  
 TGATGGTAGTACCGATTCTTGCTCCAAAAGACGCAAGTCGGAAGTCTTCCCCCAGCATTC

4022 ProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMetAlaLeu  
 CCAGCTCGTCTCATCGTGTTCCTCGATCTGGGCGTGCAGCGTGTGCGAAAAGATGGCTTTG  
 GGTGAGCAGAGTAGCACAAGGGGCTAGACCCGCACGCGCACACGCTTTTCTACCGAAAC

4082 TyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPheGlnTyr  
 TACGACGTGGTTACAAAGCTCCCCTTGGCCGTGATGGGAAGCTCCTACGGATTCCAATAC  
 ATGCTGCACCAATGTTTCGAGGGGAACCGGCACCTACCTTCGAGGATGCCTAAGGTTATG

4142 SerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThrProMet  
 TCACCAGGACAGCGGGTTGAATTCCTCGTGCAAGCGTGAAGTCCAAGAAAACCCCAATG  
 AGTGGTCTGTGCGCCAACTTAAGGAGCACGTTTCGCACCTTCAGGTTCTTTTGGGGTTAC  
 ^

4160 ECORI,

4202 GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr  
 GGGTCTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATCCGTACG  
 CCCAAGAGCATACTATGGGCGACGAACTGAGGTGTCAGTGACTCTCGCTGTAGGCATGC  
 ^ ^

## FIGURE 21 - Page 8

4229 DRD1, 4236 ALWN1,  
GluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIleLysSer  
4262 GAGGAGGCAATCTACCAATGTTGTGACCTCGACCCCAAGCCCGGTGGCCATCAAGTCC  
CTCCTCCGTTAGATGGTTACAACACTGGAGCTGGGGGTTCGGGCGCACCGGTAGTTCAGG  
4301 BGLI, 4308 BALI,  
LeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsnCysGly  
4322 CTCACCGAGAGGCTTTATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAGAACTGCGGC  
GAGTGGCTCTCCGAAATACAACCCCGGAGAAATGGTTAAGTTCCCCCTCTTGACGCCG  
4345 APAI,  
TyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys  
4382 TATCGCAGGTGCCGCGCGAGCGGCGTACTGACAACCTAGCTGTGGTAACACCCTCACTTGC  
ATAGCGTCCACGGCGCGCTCGCCCATGACTGTTGATCGACACCATTGTGGGAGTGAACG  
TyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMetLeuVal  
4442 TAATCAAGGCCCCGGGCAGCCTGTGAGCCGCGAGGCTCCAGGACTGCACCATGCTCGTG  
ATGTAGTTCGGGGCCCGTCGGACAGCTCGGCGTCCCGAGGTCTGACGTGGTACGAGCAC  
4452 SMAI XMAI,  
CysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAlaAlaSer  
4502 TGTGGCGACGACTTAGTCGTTATCTGTGAAAGCGCGGGGTCCAGGAGGACGCGCGGAGC  
ACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCCAGGTCTCCTGCGCCGCTCG  
4508 DRD1, 4511 TTH3I,  
LeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspProProGln  
4562 CTGAGAGCCTTCACGGAGGCTATGACCAGGTACTCCGCCCCCCTGGGGACCCCCACAA  
GACTCTCGGAAGTGCTCCGATACTGGTCCATGAGGCGGGGGGACCCCTGGGGGGTGT  
ProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAlaHisAsp  
4622 CCAGAATACGACTTGGAGCTCATAACATCATGCTCCTCCAACGTGTGAGTCCCCACGAC  
GGTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTTGCACAGTCAGCGGGTGTCT  
4637 SACI,  
GlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAlaArgAla  
4682 GGCGCTGGAAGAGGGTCTACTACCTACCCGTGACCCTACAACCCCCCTCGCGAGAGCT  
CCGCGACCTTCTCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGAGCGCTCTCGA  
4731 NRUI,  
AlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIleMetPhe  
4742 GCGTGGGAGACAGCAAGACACACTCCAGTCAATTCCTGGCTAGGCAACATAATCATGTTT  
CGCACCTCTGTGTTCTGTGTGAGGTGAGTTAAGGACCGATCCGTTGTATTAGTACAAA  
AlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeuIleAla  
4802 GCCCCACACTGTGGGCGAGGATGATACTGATGACCCATTTCTTTAGCGTCCTTATAGCC  
CGGGGGTGTGACACCGCTCCTACTATGACTACTGGGTAAAGAAATCGCAGGAATATCGG  
4806 PFLM1, 4807 DRA3,  
ArgAspGlnLeuGluGlnAlaLeuAspCysGluIleTyrGlyAlaCysTyrSerIleGlu

## FIGURE 21 - Page

4862 AGGGACCAGCTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCCATAGAA  
TCCCTGGTCGAACTTGTCCGGGAGCTAACGCTCTAGATGCCCCGGACGATGAGGTATCTT  
4893 BGL2,  
ProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSerLeuHis  
4922 CCACTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCACTCCAC  
GGTGACCTAGATGGAGGTTAGTAAGTTTCTGAGGTACCGGAGTTCGCGTAAAAGTGAGGTG  
4954 NCOI,  
SerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGlyValPro  
4982 AGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGCATGCCTCAGAAAACCTGGGGTACCG  
TCAATGAGAGGTCCACTTTAGTTATCCCACCGGCGTACGGAGTCTTTTGAACCCCATGGC  
5015 SPHI, 5035 KPNI,  
ProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAlaArgGly  
5042 CCCTTGCGAGCTTGGAGACACCGGGCCCGGAGCGTCCGCGCTAGGCTTCTGGCCAGAGGA  
GGGAACGCTCGAACCTCTGTGGCCCGGCGCTCGCAGGCGCGATCCGAAGACCGGTCTCTT  
5064 APAI, 5091 BALI,  
GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys  
5102 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAGCTCAA  
CCGTCCCGACGGTATACACCGTTCATGGAGAAGTTGACCCGTCATTCTTGTTCGAGTTT  
5113 NDEI,  
LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr  
5162 CTACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTCACGGCTGGCTAC  
GAGTGAGGTTATCGCCGGCGACCGGTTCGACCTGAACAGGCCGACCAAGTGCCGACCGATG  
5174 NOTI, 5175 EAGI XMA3, 5182 BALI, 5186 PVU2,  
SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys  
5222 AGCGGGGGAGACATTTATCACAGCGTGTCTCATGCCCGGGCCCGCTGGATCTGGTTTTGC  
TCGCCCCCTCTGTAAATAGTGTGCACAGAGTACGGGCGGGGCGACCTAGACCAAACG  
5240 DRA3,  
LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgMetSerThrAsn  
5282 CTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCCAACCGAATGAGCACGAAT  
GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTGGCTTACTCGTGCTTA  
5295 PSTI,  
ProLysProGlnArgLysThrLysArgAsnThrAsnArgArgProGlnAspValLysPhe  
5342 CCTAAACCTCAAAGAAAGACCAAACGTAACACCAACCGGCGGCCGAGGACGTCAAGTTC  
GGATTGGAGTTTCTTTCTGGTTTGCATTGTGGTTGGCCGCGCGCTCTGCAGTTCAAG  
5380 NOTI, 5381 EAGI XMA3, 5390 AAT2, 5401 SMAI XMAI,  
ProGlyGlyGlyGlnIleValGlyGlyValTyrLeuLeuProArgArgGlyProArgLeu  
5402 CCGGGTGGCGGTGAGATCGTTGGTGGAGTTTACTTGTGGCGCGCAGGGGGCCCTAGATTG  
GGCCACCGCCAGTCTAGCAACCACCTCAAATGAACAACGGCGCGTCCCCGGGATCTAAC

## FIGURE 21 - Page 10

5449 APAI,

5462 GlyValArgAlaThrArgLysThrSerGluArgSerGlnProArgGlyArgArgGlnPro  
GGTGTGCGCGCGACGAGAAAGACTTCCGAGCGGTGCGAACCTCGAGGTAGACGTCAGCCT  
CCACACGCGCGCTGCTCTTTCTGAAGGCTCGCCAGCGTTGGAGCTCCATCTGCAGTCGGA

5467 BSSH2, 5478 XMNI, 5502 XHOI, 5511 AAT2,

5522 IleProLysAlaArgArgProGluGlyArgThrTrpAlaGlnProGlyTyrProTrpPro  
ATCCCCAAGGCTCGTCGGCCCGAGGGCAGGACCTGGGCTCAGCCCGGTACCTTGGCCC  
TAGGGGTTCCGAGCAGCCGGGCTCCCGTCCTGGACCCGAGTCGGGCCCATGGGAACCGGG

5548 ALWN1, 5558 ESP1, 5564 SMAI XMAI, 5568 KPNI,

5582 LeuTyrGlyAsnGluGlyCysGlyTrpAlaGlyTrpLeuLeuSerProArgGlySerArg  
CTCTATGGCAATGAGGGCTGCGGGTGGCGGGATGGCTCCTGTCTCCCGTGGCTCTCGG  
GAGATACCGTTACTCCCGACGCCACCCGCCCTACCGAGGACAGAGGGGCACCGAGAGCC

5642 ProSerTrpGlyProThrAspProArgArgArgSerArgAsnLeuGlyLysValIleAsp  
CCTAGCTGGGGCCCCACAGACCCCGGCGTAGGTCGCGCAATTTGGGTAAGGTCATCGAT  
GGATCGACCCCGGGGTGTCTGGGGGCCGATCCAGCGCGTTAAACCCATTCCAGTAGCTA

5650 APAI, 5696 CLAI,

5702 ThrLeuThrCysGlyPheAlaAspLeuMetGlyTyrIleProLeuValOC AM  
ACCCTTACGTGCGGCTTCGCCGACCTCATGGGGTACATACCGCTCGTCTAATAGTCGAC  
TGGGAATGCACGCCAAGCGGCTGGAGTACCCCATGTATGGCGAGCAGATTATCAGCTG

5724 HGIE2, 5755 SALI,

## FIGURE 22 - Page 1

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn  
 2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC  
 TCGAATGTTTTGTTTTACCGACGTATACGTGAGTCCCGATATCCACGATCATGAGTTG  
 ^ ^  
 1 HIND3, 24 NDEI, 52 SCAI,

ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp  
 62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT  
 GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCGAGTACCCTAGCTA  
 ^  
 116 CLAI,

ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr  
 122 CCTAACATCAGGACCGGGTGAGAACAAATTACCACTGGCAGCCCCATCACGTACTCCACC  
 GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGCATGAGGTGG

TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys  
 182 TACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT  
 ATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGGAATACTGTATTATTAAACA

AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln  
 242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA  
 CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAAGTGGTT

AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal  
 302 GCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC  
 CGTCTCTGACGCCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCGAGGCG  
 ^  
 303 ALWN1,

ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe  
 362 ACTGTGCCCCATCCCAACATCGAGGAGTTGCTCTGTCCACCACCGAGAGATCCCTTTT  
 TGACACGGGGTAGGGTTGTAGCTCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA

TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis  
 422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTCTGTCAT  
 ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA

## FIGURE 22 - Page 2

SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal  
 482 TCAAAGAAGAAGTGCACGAACTCGCCGCAAAGCTGGTCGCATTGGGCATCAATGCCGTG  
 AGTTTCTTCTTCACGCTGCTTGAGCGCGCTTTCGACCAGCGTAACCCGTAGTTACGGCAC

AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal  
 542 GCCTACTACCGCGGTCTTGACGTGTCCGTCAATCCCGACCAGCGCGCATGTTGTCGTCGTG  
 CGGATGATGGCGCCAGAACTGCACAGGCAGTAGGGCTGGTCGCCGCTACAACAGCAGCAC

550 SAC2, 560 DRD1,

AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn  
 602 GCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGACTGCAAT  
 CGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTGACGTTA

615 BSPH1,

ThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGluThrIle  
 662 ACGTGTGTACCCAGACAGTCGATTTTCAGCCTTGACCCTACCTTCACCATGAGACAATC  
 TGCACACAGTGGGTCTGTGAGCTAAAGTCGGAAGTGGGATGGAAGTGGTAACTCTGTTAG

ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys  
 722 ACGCTCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGGGGGAAG  
 TCGAGGGGGTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCCTGACCGTCCCCCTTC

ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer  
 782 CCAGGCATCTACAGATTTGTGGCACCGGGGAGCGCCCCCTCCGGCATGTTTCGACTCGTCC  
 GGTCCGTAGATGTCTAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTGAGCAGG

816 BGLI, 833 DRD1,

ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr  
 842 GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCGCCGAGACT  
 CAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAGTGCGGGCGGCTCTGA

881 SACI,

ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu  
 902 ACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGACCATCTT  
 TGTCATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCCTGGTAGAA

931 SMAI XMAI,

GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln  
 962 GAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCCCACTTTCTATCCCAG  
 CTTAAACCCCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC

985 STUI,

ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla  
 1022 ACAAGCAGAGTGGGGAGAACCTTCCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT  
 TGTTTCGTCTACCCCTCTTGAAGGAATGGACCATCGCATGGTTCGGTGGCACACGCGA

1069 DRA3,

ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys  
 1082 AGGGCTCAAGCCCCTCCCCATCGTGGGACCAGATGTGGAAGTGTTTGATTCCGCTCAAG

## FIGURE 22 - Page 3

TCCCGAGTTCGGGGAGGGGGTAGCACCTGGTCTACACCTTCACAACTAAGCGGAGTTC

ProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsnGluIle  
 1142 CCCACCCTCCATGGGCCAACACCCTGCTATACAGACTGGGCGCTGTTCAGAATGAAATC  
 GGGTGGGAGGTACCCGGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTACTTTAG  
 1150 NCOI,

ThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeuGluVal  
 1202 ACCCTGACGCACCCAGTCACCAAATACATCATGACATGCATGTCGGCCGACCTGGAGGTC  
 TGGGACTGCGTGGGTCAGTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGACCTCCAG  
 1230 BSPH1, 1234 DRD1, 1237 AVA3, 1245 EAG1 XMA3, 1250 DRD1,

ValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyrCysLeu  
 1262 GTCACGAGCACCTGGGTGCTCGTTGGCGGCGTCCTGGCTGCTTTGGCCGCGTATTGCCTG  
 CAGTGCTCGTGGACCCACGAGCAACCGCCGAGGACCGACGAAACCGGCGCATAACGGAC

SerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAlaIleIle  
 1322 TCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCGTCTGTCCGGGAAGCCGGCAATCATA  
 AGTTGTCCGACGCACCAAGTATCACCCGTCCCAGCAGAACAGGCCCTTCGGCCGTTAGTAT  
 1369 NAEI,

ProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGlnHisLeu  
 1382 CCTGACAGGGAAGTCTCTACCGAGAGTTCGATGAGATGGAAGAGTGCTCTCAGCACTTA  
 GGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCAGGAGAGTCGTGAAT  
 1385 DRD1,

ProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeuGlyLeu  
 1442 CCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAGAAGGCCCTCGGCCCTC  
 GGCATGTAGCTCGTTCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCCGGGAGCCGGAG

LeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsnTrpGln  
 1502 CTGCAGACCGCGTCCCGTCAGGCAGAGGTTATCGCCCCTGCTGTCCAGACCAACTGGCAA  
 GAGTCTGGCGCAGGGCAGTCCGTCTCCAATAGCGGGGACGACAGGTCTGGTTGACCGTT  
 1502 PSTI, 1507 TTH3I,

LysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGlnTyrLeu  
 1562 AAACTCGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAATACTTG  
 TTTGAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCCTATGTTATGAAC  
 1565 XHOI, 1586 NDEI,

AlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPheThrAla  
 1622 GCGGGCTTGTCAACGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTTACAGCT  
 CGCCCCAACAGTTGCGACGGACCATTTGGGGCGGTAACGAAGTAACCTACCGAAAATGTCGA  
 1643 BSTE2, 1677 ALWN1 PVU2,

AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp  
 1682 GCTGTCAACAGCCCACTAACCCTAGCCAAACCTCCTCTTCAACATATTGGGGGGGTGG  
 CGACAGTGGTGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC

## FIGURE 22 - Page 4

ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla  
 1742 GTGGCTGCCAGCTCGCCGCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT  
 CACCGACGGGTCGAGCGGGGGGCCACGGCGATGACGGAAACACCCGCGACCGAATCGA  
 1794 ESP1,  
 GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr  
 1802 GGCGCCGCCATCGGCAGTGTGGACTGGGGAAGGTCCTCATAGACATCCTTGCAGGGTAT  
 CCGCGGCGGTAGCCGTCACAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCCAT  
 1802 KAS1 NARI,  
 GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer  
 1862 GGCGCGGGCGTGCGGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCTCC  
 CCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG  
 1878 SACI, 1899 BSPH1,  
 ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly  
 1922 ACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCGTAGTCGGC  
 TGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCATCAGCCG  
 1928 TTH3I,  
 ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp  
 1982 GTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCGGGCGAGGGGGCAGTGCACTGG  
 CACCAGACACGTCGTTATGACGCGGCCGTGCAACCGGGCCGCTCCCCCGTCACGTCACC  
 2004 NAEI, 2017 SMAI XMAI,  
 MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal  
 2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTTCCCCACGCACTACGTG  
 TACTTGGCCGACTATCGGAAGCGGAGGGCCCTTGGTACAAAGGGGGTGCGTGATGCAC  
 2067 SMAI XMAI, 2093 DRA3,  
 ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln  
 2102 CCGGAGAGCGATGCAGCTGCCCGCGTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG  
 GGCTCTCGCTACGTCGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACATTGGGTC  
 2115 PVU2, 2159 ALWN1,  
 LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer  
 2162 CTCCTGAGGCGACTGCACCACTGGATAAGCTCGGAGTGTAACCACTCCATGCTCCGGTTCC  
 GAGGACTCCGCTGACGTGGTCACCTATTTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG  
 2164 MST2, 2220 ECON1,  
 TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu  
 2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACCTGGCTA  
 ACCGATTCCCTGTAGACCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGGACCGAT  
 LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr  
 2282 AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCTTTGTGTCTGCCAGCGCGGGTAT  
 TTTGATTGAGTACGGTGTGACGGACCCTAGGGGAAACACAGGACGGTCGCGCCCAT  
 2285 ESP1, 2300 PVU2, 2310 BAMHI,



## FIGURE 22 - Page 5

2342 LysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAlaGluIle  
 AAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC  
 TTCCCCAGACCGCTCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG

2402 ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet  
 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCCTAGGACCTGCAGGAACATG  
 TGACCTGTACAGTTTTTGGCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCCTTGTAC  
 2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,

2462 TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla  
 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGGCCCTGTACCCCCCTTCCTGCG  
 ACCTCACCTGGAAGGGGTAATTACGGATGTGGTGCCCGGGGACATGGGGGGAAGGACGC  
 2480 ASE1, 2497 APAI,

2522 ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln  
 CCGAACTACACGTTTCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATAAGGCAG  
 GGCTTGATGTGCAAGCGGATACCTCCCACAGACGTCTCCTTATGCACCTCTATTCCGTC  
 2553 PSTI,

2582 ValGlyAspPheHisTyrValThrGlyMetThrThrAspAsnLeuLysCysProCysGln  
 GTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCCGTGCCAG  
 CACCCCTGAAGGTGATGCACTGCCCATACTGATGACTGTTAGAATTTACGGGCACGGTC  
 2594 DRA3,

2642 ValProSerProGluPhePheThrGluLeuAspGlyValArgLeuHisArgPheAlaPro  
 GTCCCATCGCCCGAATTTTTCACAGAATTGGACGGGGTGCGCCTACATAGGTTTGCGCCC  
 CAGGGTAGCGGGCTTAAAAAGTGTCTTAACCTGCCCCACGCGGATGTATCCAAACGCGGG

2702 ProCysLysProLeuLeuArgGluGluValSerPheArgValGlyLeuHisGluTyrPro  
 CCCTGCAAGCCCTTGCTGCGGGAGGAGGTATCATTAGAGTAGGACTCCACGAATACCCG  
 GGGACGTTGCGGAACGACGCCCTCCTCCATAGTAAGTCTCATCTGAGGTGCTTATGGGC  
 2757 HGIE2,

2762 ValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSerMetLeu  
 GTAGGGTCGCAATTACCTTGCGAGCCCGAACCGGACGTGGCCGTGTTGACGTCCATGCTC  
 CATCCCAGCGTTAATGGAACGCTCGGGCTTGGCCTGCACCGGCACAACCTGCAGGTACGAG  
 2809 AAT2,

2822 ThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGlySerPro  
 ACTGATCCCTCCCATATAACAGCAGAGCGCGCGGGCGAAGGTTGGCGAGGGGATCACCC  
 TGACTAGGGAGGGTATATTGTCGTCTCCGCCGGCCCGCTCCAACCGCTCCCTTAGTGGG  
 2850 EAG1 XMA3,

2882 ProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAlaThrCys  
 CCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCAACTTGC  
 GGGAGACACCGGTCGAGGAGCCGATCGGTCGATAGGCGAGGTAGAGAGTTCCGTTGAACG  
 2889 BALI, 2903 NHEI,

## FIGURE 22 - Page 6

ThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuLeuTrpArgGln  
 2942 ACCGCTAACCATGACTCCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAG  
 TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGGTTGGAGGATACCTCCGTC  
 ^ ^  
 2966 ESP1, 2969 SACI,  
 GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer  
 3002 GAGATGGGCGGCAACATCACCAGGGTTGAGTCAGAAAACAAAGTGGTGATTCTGGACTCC  
 CTCTACCCGCCGTTGTAGTGGTCCCACTCAGTCTTTTGTTCACCACTAAGACCTGAGG  
 PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu  
 3062 TTCGATCCGCTTGTGGCGGAGGAGGACGAGCGGGAGATCTCCGTACCCGCAGAAATCCTG  
 AAGCTAGGCGAACACCGCCTCCTCCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC  
 ^  
 3096 BGL2,  
 ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro  
 3122 CGGAAGTCTCGGAGATTGCCCCAGGCCCTGCCCGTTTGGGCGCGGCCGACTATAACCCC  
 GCCTTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGGCCTGATATTGGGG  
 ^ ^  
 3143 ALWN1, 3164 EAG1 XMA3,  
 ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro  
 3182 CCGCTAGTGGAGACGTGGAAAAAGCCCGACTACGAACCACCTGTGGTCCATGGCTGCCCG  
 GGCGATCACCTCTGCACCTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCGACGGGC  
 ^ ^  
 3217 HGIE2, 3229 NCOI,  
 LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu  
 3242 CTTCCACCTCAAAGTCCCCTCCTGTGCCTCCGCTCGGAAGAAGCGGACGGTGGTCCTC  
 GAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCACCAGGAG  
 ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSer  
 3302 ACTGAATCAACCCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGCAGCTCC  
 TGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCGTCGAGG  
 ^ ^  
 3332 SACI, 3346 HIND3,  
 SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly  
 3362 TCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCGCCCTTCTGGC  
 AGTTGAAGGCCGTAATGCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG  
 CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluPro  
 3422 TGCCCCCCCCGACTCCGACGCTGAGTCCTATTCTCCATGCCCCCCTGGAGGGGGAGCCT  
 ACGGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA  
 ^  
 3437 EAM11051,  
 GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu  
 3482 GGGGATCCGGATCTTAGCGACGGGTCATGGTCAACGGTCAGTAGTGAGGCCAACCGGGAG  
 CCCCTAGGCCCTAGAATCGCTGCCAGTACCAGTTGCCAGTCATCACTCCGGTTGCGCCTC  
 ^ ^ ^  
 3484 BAMHI, 3485 BSAB1, 3487 BSPE1,  
 AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla  
 3542 GATGTCGTGTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCACCCCGTGCGCC  
 CTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCGTGAGCAGTGGGGCACGCGG

## FIGURE 22 - Page 7

3589 DRA3, 3600 SAC2,

AlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHisHisAsn  
 3602 GCGGAAGAACAGAACTGCCCATCAATGCACTAAGCAACTCGTTGCTACGTCACCACAAT  
 CGCCTTCTTGTCTTTGACGGGTAGTTACGTGATTCTGTTGAGCAACGATGCAGTGGTGTTA

3611 ALWN1, 3655 PFLM1,

LeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThrPheAsp  
 3662 TTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAAAGTCACATTTGAC  
 AACCACATAAGGTGGTGGAGTGCCTCACGAACGGTTTCCGCTTCTTTTCAGTGTAAGTG

3681 DRA3,

ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla  
 3722 AGACTGCAAGTTCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCAGCGCGG  
 TCTGACGTTCAAGACCTGTCGGTAATGGTCTGCATGAGTTCCTCCAATTCGTCGCCCG

SerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrProProHis  
 3782 TCAAAAGTGAAGGCTAACTTGCTATCCGTAGAGGAAGCTTGACGCTGACGCCCCACAC  
 AGTTTTCACTTCCGATTGAACGATAGGCATCTCCTTCGAACGTGCGACTGCGGGGGTG

3816 HIND3,

SerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArgLysAla  
 3842 TCAGCCAAATCCAAGTTTGGTTATGGGGCAAAGACGTCCGTTGCCATGCCAGAAAGGCC  
 AGTCGGTTTAGGTTCAAACCAATACCCCGTTTCTGCAGGCAACGGTACGGTCTTTCCGG

3875 AAT2, 3890 BGLI,

ValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrProIleAsp  
 3902 GTAACCCACATCAACTCCGTGTGGAAGACCTTCTGGAAGACAATGTAACCAATAGAC  
 CATTGGGTGTAGTTGAGGCACACCTTTCTGGAAGACCTTCTGTTACATTGTGGTTATCTG

ThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGlyArgLys  
 3962 ACTACCATCATGGCTAAGAACGAGGTTTTCTGCGTTTCAGCCTGAGAAGGGGGTCGTAAG  
 TGATGGTAGTACCGATTCTTGCTCCAAAAGACGCAAGTCGGACTCTTCCCCCAGCATTC

ProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMetAlaLeu  
 4022 CCAGCTCGTCTCATCGTGTTCCTCGATCTGGGCGTGCGCGTGTGCGAAAAGATGGCTTTG  
 GGTGAGCAGAGTAGCACAAAGGGGCTAGACCCGCACGCGCACAGCTTTTCTACCGAAAC

TyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPheGlnTyr  
 4082 TACGACGTGGTTACAAAGCTCCCCTTGCCGTGATGGGAAGCTCCTACGGATTCCAATAC  
 ATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCTTCGAGGATGCCTAAGGTTATG

SerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThrProMet  
 4142 TCACCAGGACAGCGGGTTGAATTCCTCGTCAAGCGTGGAAGTCCAAGAAAACCCCAATG  
 AGTGGTCTGTCGCCCACTTAAGGAGCAGTTCGCACCTTCAGGTTCTTTGGGGTTAC

4160 ECORI,

GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr  
 4202 GGGTTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATCCGTACG  
 CCAAGAGCATACTATGGGCGACGAACTGAGGTGTCACTGACTCTCGCTGTAGGCATGC

## FIGURE 22 - Page 8

4229 DRD1, 4236 ALWN1,  
 GluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIleLysSer  
 4262 GAGGAGGCAATCTACCAATGTTGTGACCTCGACCCCAAGCCCGCTGGCCATCAAGTCC  
 CTCTCCGTTAGATGGTTACAACACTGGAGCTGGGGGTTCTGGGCGCACCGGTAGTTCAGG  
 4301 BGLI, 4308 BALI,  
 LeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsnCysGly  
 4322 CTCACCGAGAGGCTTTATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAGAACTGCGGC  
 GAGTGGCTCTCCGAAATACAACCCCGGGGAGAATGGTTAAGTTCCTCCCTCTTGACGCCG  
 4345 APAI,  
 TyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys  
 4382 TATCGCAGGTGCCGCGGAGCGGCGTACTGACAACTAGCTGTGGTAACACCCTCACTTGC  
 ATAGCGTCCACGGCGCGCTCGCCCATGACTGTTGATCGACACCATTGTGGGAGTGAACG  
 TyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMetLeuVal  
 4442 TACATCAAGGCCCGGGCAGCCTGTGAGCCGCGAGGCTCCAGGACTGCACCATGCTCGTG  
 ATGTAGTTCGGGGCCCGTCGGACAGCTCGGCGTCCCGAGGTCCTGACGTGGTACGAGCAC  
 4452 SMAI XMAI,  
 CysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAlaAlaSer  
 4502 TGTGGCGACGACTTAGTCGTTATCTGTGAAAGCGCGGGGGTCCAGGAGGACGCGCGGAGC  
 ACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCAGGTCTCTGCGCGCTCG  
 4508 DRD1, 4511 TTH3I,  
 LeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspProProGln  
 4562 CTGAGAGCCTTCACGGAGGCTATGACCAGGTACTCCGCCCCCTGGGGACCCCCACAA  
 GACTCTCGGAAGTGCCTCCGATACTGGTCCATGAGGCGGGGGGACCCCTGGGGGGTGT  
 ProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAlaHisAsp  
 4622 CCAGAATACGACTTGGAGCTCATAACATCATGCTCCTCCAACGTGTGAGTCCCCACGAC  
 GGTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTTGCACAGTCAGCGGGTGCTG  
 4637 SACI,  
 GlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAlaArgAla  
 4682 GGCGCTGGAAAGAGGGTCTACTACCTCACCCGTGACCCTACAACCCCTCGCGAGAGCT  
 CCGCGACCTTCTCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGGAGCGCTCTCGA  
 4731 NRUI,  
 AlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIleMetPhe  
 4742 GCGTGGGAGACAGCAAGACACACTCCAGTCAATTCCTGGCTAGGCAACATAATCATGTTT  
 CGCACCTCTGTCGTTCTGTGTGAGGTGAGTTAAGGACCGATCCGTTGTATTAGTACAAA  
 AlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeuIleAla  
 4802 GCCCCACACTGTGGGCGAGGATGATACTGATGACCCATTTCTTTAGCGTCTTATAGCC  
 CGGGGTGTGACACCCGCTCTACTATGACTACTGGGTAAAGAAATCGCAGGAATATCGG  
 4806 PFLM1, 4807 DRA3,  
 ArgAspGlnLeuGluGlnAlaL uAspCysGluIleTyrGlyAlaCysTyrSerIleGlu

## FIGURE 22 - Page 9

4862 AGGGACCAGCTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCCATAGAA  
TCCCTGGTCGAACCTGTCCGGGAGCTAACGCTCTAGATGCCCCGGACGATGAGGTATCTT  
4893 BGL2,  
ProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSerLeuHis  
4922 CCACTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCACTCCAC  
GGTGACCTAGATGGAGGTTAGTAAGTTTCTGAGGTACCGGAGTCGCGTAAAAGTGAGGTG  
4954 NCOI,  
SerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGlyValPro  
4982 AGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGCATGCCTCAGAAAACCTGGGGTACCG  
TCAATGAGAGGTCCACTTTAGTTATCCACCGGCGTACGGAGTCTTTTGAACCCCATGGC  
5015 SPHI, 5035 KPNI,  
ProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAlaArgGly  
5042 CCCTTGGCAGCTTGGAGACACCGGGCCCGAGCGTCCGCGCTAGGCTTCTGGCCAGAGGA  
GGGAACGCTCGAACCTCTGTGGCCCGGGCCTCGCAGGCGCGATCCGAAGACCGGTCTCCT  
5064 APAI, 5091 BALI,  
GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys  
5102 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAGCTCAAA  
CCGTCCCGACGGTATACACCGTTCATGGAGAAGTTGACCCGTCATTCTGTTTCGAGTTT  
5113 NDEI,  
LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr  
5162 CTCCTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTCACGGCTGGCTAC  
GAGTGAGGTTATCGCCGGCGACCGGTTCGACCTGAACAGGCCGACCAAGTGCCGACCGATG  
5174 NOTI, 5175 EAGI XMA3, 5182 BALI, 5186 PVU2,  
SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys  
5222 AGCGGGGGAGACATTTATCACAGCGTGTCTCATGCCGGGCCCGCTGGATCTGGTTTTCG  
TCGCCCCCTCTGTAAATAGTGTGCGACAGAGTACGGGCCGGGGCGACCTAGACCAAACG  
5240 DRA3,  
LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgMetSerThrAsn  
5282 CTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCAACCGAATGAGCACGAAT  
GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTGGCTTACTCGTGCTTA  
5295 PSTI,  
ProLysProGlnArgLysThrLysArgAsnThrAsnArgArgProGlnAspValLysPhe  
5342 CCTAAACCTCAAAGAAAGACCAAACGTAACACCAACCGCGGCCGAGGACGTCAAGTTC  
GGATTTGGAGTTTCTTTCTGGTTTGCATTGTGGTTGGCCGCCGGCGTCTGCAGTTCAAG  
5380 NOTI, 5381 EAGI XMA3, 5390 AAT2, 5401 SMAI XMAI,  
ProGlyGlyGlyGlnIleValGlyGlyValTyrLeuLeuProArgArgGlyProArgLeu  
5402 CCGGGTGGCGGTCAGATCGTTGGTGGAGTTTACTTGTGTCGCGCAGGGGCCCTAGATTG  
GGCCACCGCCAGTCTAGCAACCACCTCAAATGAACAACGGCGCGTCCCGGGATCTAAC

**FIGURE 22 - Page 10**

5449 APAI,

GlyValArgAlaThrArgLysThrSerGluArgSerGlnProArgGlyArgArgGlnPro  
 5462 GGTGTGCGCGCGACGAGAAAGACTTCCGAGCGGTCGCAACCTCGAGGTAGACGTCAGCCT  
 CCACACGCGCGCTGCTCTTTCTGAAGGCTCGCCAGCGTTGGAGCTCCATCTGCAGTCGGA

5467 BSSH2, 5478 XMNI, 5502 XHOI, 5511 AAT2,

IleProLysAlaArgArgProGluGlyArgThrTrpAlaGlnProGlyTyrProTrpPro  
 5522 ATCCCCAAGGCTCGTCGGCCCCGAGGGCAGGACCTGGGCTCAGCCCGGGTACCCTTGGCCC  
 TAGGGGTTCCGAGCAGCCGGGCTCCCGTCCTGGACCCGAGTCGGGCCCCATGGGAACCGGG

5548 ALWN1, 5558 ESP1, 5564 SMAI XMAI, 5568 KPNI,

LeuTyrGlyAsnGluGlyCysGlyTrpAlaGlyTrpLeuLeuSerProArgGlySerArg  
 5582 CTCTATGGCAATGAGGGCTGCGGGTGGGCGGGATGGCTCCTGTCTCCCGTGGCTCTCGG  
 GAGATACCGTTACTCCCGACGCCACCCGCCCTACCGAGGACAGAGGGCACCGAGAGCC

ProSerTrpGlyProThrAspProArgArgArgSerArgAsnLeuGlyLysValIleAsp  
 5642 CCTAGCTGGGGCCCCACAGACCCCGGCGTAGGTGCGCAATTGGGTAAGGTCATCGAT  
 GGATCGACCCCGGGGTGTCTGGGGCCGCATCCAGCGGTTAAACCCATTCCAGTAGCTA

5650 APAI, 5696 CLAI,

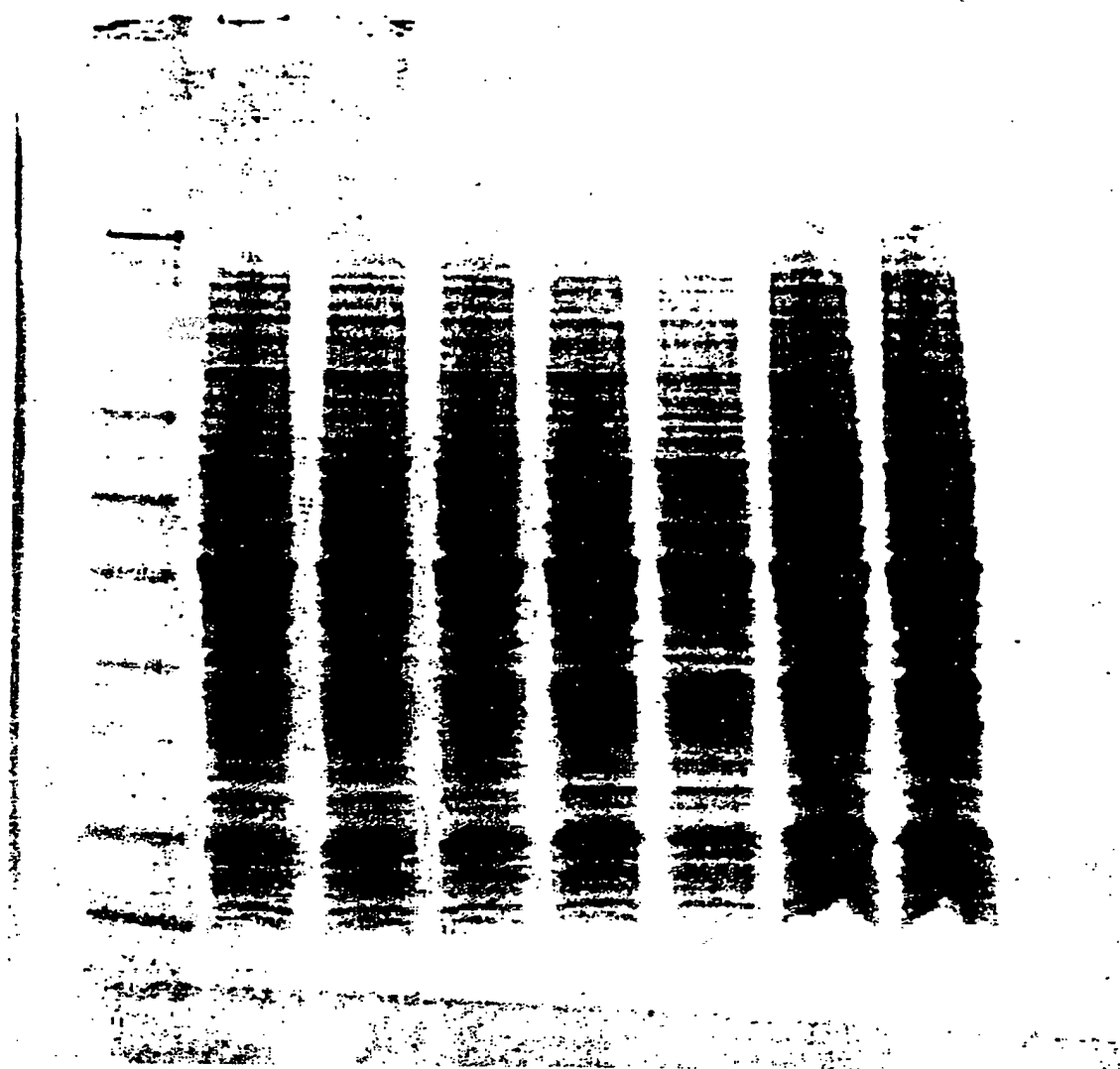
ThrLeuThrCysGlyPheAlaAspLeuMetGlyTyrIleProLeuValGlyAlaProLeu  
 5702 ACCCTTACGTGCGGCTTCGCCGACCTCATGGGGTACATACCGCTCGTCGGCGCCCTCTT  
 TGGAATGCACGCCGAAGCGGCTGGAGTACCCCATGTATGGCGAGCAGCCGCGGGGAGAA

5724 HGIE2, 5750 KAS1 NARI, 5756 ECON1,

GlyGlyAlaAlaArgAlaOC AM  
 5762 GGAGGCGCTGCCAGGGCCTAATAGTCGAC  
 CCTCCGCGACGGTCCCGGATTATCAGCTG

5785 SALI,

FIGURE 23



## SEQUENCE LISTING

<110> CHIRON CORPORATION et al.

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tggcgggtgt cggggctggc ttaactatgc ggcatcagag cagattgtac tgagagtgc 180
ccatatgaag ctttttgcaa aagcctaggc ctccaaaaaa gcctcctcac tacttctgga 240
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 Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys  
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 gct cat ggg atc gat cct aac atc agg acc ggg gtg aga aca att acc 2127  
 Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr  
 35 40 45  
 act ggc agc ccc atc acg tac tcc acc tac ggc aag ttc ctt gcc gac 2175  
 Thr Gly Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp  
 50 55 60  
 ggc ggg tgc tgc ggg ggc gct tat gac ata ata att tgt gac gag tgc 2223  
 Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys  
 65 70 75  
 cac tcc acg gat gcc aca tcc atc ttg ggc att ggc act gtc ctt gac 2271  
 His Ser Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp  
 80 85 90

|                                                                 |      |
|-----------------------------------------------------------------|------|
| caa gca gag act gcg ggg gcg aga ctg gtt gtg ctc gcc acc gcc acc | 2319 |
| Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr |      |
| 95 100 105 110                                                  |      |
| cct ccg ggc tcc gtc act gtg ccc cat ccc aac atc gag gag gtt gct | 2367 |
| Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala |      |
| 115 120 125                                                     |      |
| ctg tcc acc acc gga gag atc cct ttt tac ggc aag gct atc ccc ctc | 2415 |
| Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu |      |
| 130 135 140                                                     |      |
| gaa gta atc aag ggg ggg aga cat ctc atc ttc tgt cat tca aag aag | 2463 |
| Glu Val Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys |      |
| 145 150 155                                                     |      |
| aag tgc gac gaa ctc gcc gca aag ctg gtc gca ttg ggc atc aat gcc | 2511 |
| Lys Cys Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala |      |
| 160 165 170                                                     |      |
| gtg gcc tac tac cgc ggt ctt gac gtg tcc gtc atc ccg acc agc ggc | 2559 |
| Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly |      |
| 175 180 185 190                                                 |      |
| gat gtt gtc gtc gtg gca acc gat gcc ctc atg acc ggc tat acc ggc | 2607 |
| Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly |      |
| 195 200 205                                                     |      |
| gac ttc gac tcg gtg ata gac tgc aat acg tgt gtc acc cag aca gtc | 2655 |
| Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val |      |
| 210 215 220                                                     |      |
| gat ttc agc ctt gac cct acc ttc acc att gag aca atc acg ctc ccc | 2703 |
| Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro |      |
| 225 230 235                                                     |      |
| caa gat gct gtc tcc cgc act caa cgt cgg ggc agg act ggc agg ggg | 2751 |
| Gln Asp Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly |      |
| 240 245 250                                                     |      |
| aag cca ggc atc tac aga ttt gtg gca ccg ggg gag cgc ccc tcc ggc | 2799 |
| Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly |      |
| 255 260 265 270                                                 |      |
| atg ttc gac tcg tcc gtc ctc tgt gag tgc tat gac gca ggc tgt gct | 2847 |
| Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala |      |
| 275 280 285                                                     |      |
| tgg tat gag ctc acg ccc gcc gag act aca gtt agg cta cga gcg tac | 2895 |
| Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr |      |
| 290 295 300                                                     |      |
| atg aac acc ccg ggg ctt ccc gtg tgc cag gac cat ctt gaa ttt tgg | 2943 |
| Met Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp |      |
| 305 310 315                                                     |      |
| gag ggc gtc ttt aca ggc ctc act cat ata gat gcc cac ttt cta tcc | 2991 |
| Glu Gly Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser |      |
| 320 325 330                                                     |      |

|                                                                 |      |
|-----------------------------------------------------------------|------|
| cag aca aag cag agt ggg gag aac ctt cct tac ctg gta gcg tac caa | 3039 |
| Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln |      |
| 335 340 345 350                                                 |      |
| gcc acc gtg tgc gct agg gct caa gcc cct ccc cca tgc tgg gac cag | 3087 |
| Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln |      |
| 355 360 365                                                     |      |
| atg tgg aag tgt ttg att cgc ctc aag ccc acc ctc cat ggg cca aca | 3135 |
| Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr |      |
| 370 375 380                                                     |      |
| ccc ctg cta tac aga ctg ggc gct gtt cag aat gaa atc acc ctg acg | 3183 |
| Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile Thr Leu Thr |      |
| 385 390 395                                                     |      |
| cac cca gtc acc aaa tac atc atg aca tgc atg tgc gcc gac ctg gag | 3231 |
| His Pro Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala Asp Leu Glu |      |
| 400 405 410                                                     |      |
| gtc gtc acg agc acc tgg gtg ctc gtt ggc ggc gtc ctg gct gct ttg | 3279 |
| Val Val Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu |      |
| 415 420 425 430                                                 |      |
| gcc gcg tat tgc ctg tca aca ggc tgc gtg gtc ata gtg ggc agg gtc | 3327 |
| Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val Gly Arg Val |      |
| 435 440 445                                                     |      |
| gtc ttg tcc ggg aag ccg gca atc ata cct gac agg gaa gtc ctc tac | 3375 |
| Val Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr |      |
| 450 455 460                                                     |      |
| cga gag ttc gat gag atg gaa gag tgc tct cag cac tta ccg tac atc | 3423 |
| Arg Glu Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr Ile |      |
| 465 470 475                                                     |      |
| gag caa ggg atg atg ctc gcc gag cag ttc aag cag aag gcc ctc ggc | 3471 |
| Glu Gln Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly |      |
| 480 485 490                                                     |      |
| ctc ctg cag acc gcg tcc cgt cag gca gag gtt atc gcc cct gct gtc | 3519 |
| Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala Pro Ala Val |      |
| 495 500 505 510                                                 |      |
| cag acc aac tgg caa aaa ctc gag acc ttc tgg gcg aag cat atg tgg | 3567 |
| Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys His Met Trp |      |
| 515 520 525                                                     |      |
| aac ttc atc agt ggg ata caa tac ttg gcg ggc ttg tca acg ctg cct | 3615 |
| Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro |      |
| 530 535 540                                                     |      |
| ggt aac ccc gcc att gct tca ttg atg gct ttt aca gct gct gtc acc | 3663 |
| Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ala Val Thr |      |
| 545 550 555                                                     |      |
| agc cca cta acc act agc caa acc ctc ctc ttc aac ata ttg ggg ggg | 3711 |
| Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly |      |
| 560 565 570                                                     |      |

|                                                                 |      |
|-----------------------------------------------------------------|------|
| tgg gtg gct gcc cag ctc gcc gcc ccc ggt gcc gct act gcc ttt gtg | 3759 |
| Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe Val |      |
| 575 580 585 590                                                 |      |
| ggc gct ggc tta gct ggc gcc gcc atc ggc agt gtt gga ctg ggg aag | 3807 |
| Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly Lys |      |
| 595 600 605                                                     |      |
| gtc ctc ata gac atc ctt gca ggg tat ggc gcg ggc gtg gcg gga gct | 3855 |
| Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala |      |
| 610 615 620                                                     |      |
| ctt gtg gca ttc aag atc atg agc ggt gag gtc ccc tcc acg gag gac | 3903 |
| Leu Val Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser Thr Glu Asp |      |
| 625 630 635                                                     |      |
| ctg gtc aat cta ctg ccc gcc atc ctc tcg ccc gga gcc ctc gta gtc | 3951 |
| Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val |      |
| 640 645 650                                                     |      |
| ggc gtg gtc tgt gca gca ata ctg cgc cgg cac gtt ggc ccg ggc gag | 3999 |
| Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu |      |
| 655 660 665 670                                                 |      |
| ggg gca gtg cag tgg atg aac cgg ctg ata gcc ttc gcc tcc cgg ggg | 4047 |
| Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly |      |
| 675 680 685                                                     |      |
| aac cat gtt tcc ccc acg cac tac gtg ccg gag agc gat gca gct gcc | 4095 |
| Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala |      |
| 690 695 700                                                     |      |
| cgc gtc act gcc ata ctc agc agc ctc act gta acc cag ctc ctg agg | 4143 |
| Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln Leu Leu Arg |      |
| 705 710 715                                                     |      |
| cga ctg cac cag tgg ata agc tcg gag tgt acc act cca tgc tcc ggt | 4191 |
| Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly |      |
| 720 725 730                                                     |      |
| tcc tgg cta agg gac atc tgg gac tgg ata tgc gag gtg ttg agc gac | 4239 |
| Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp |      |
| 735 740 745 750                                                 |      |
| ttt aag acc tgg cta aaa gct aag ctc atg cca cag ctg cct ggg atc | 4287 |
| Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile |      |
| 755 760 765                                                     |      |
| ccc ttt gtg tcc tgc cag cgc ggg tat aag ggg gtc tgg cga ggg gac | 4335 |
| Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp |      |
| 770 775 780                                                     |      |
| ggc atc atg cac act cgc tgc cac tgt gga gct gag atc act gga cat | 4383 |
| Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile Thr Gly His |      |
| 785 790 795                                                     |      |
| gtc aaa aac ggg acg atg agg atc gtc ggt cct agg acc tgc agg aac | 4431 |
| Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr Cys Arg Asn |      |
| 800 805 810                                                     |      |

6

|                                                                                                                                                           |      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| ccc ccg cta gtg gag acg tgg aaa aag ccc gac tac gaa cca cct gtg<br>Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu Pro Pro Val<br>1055 1060 1065 1070 | 5199 |
| gtc cat ggc tgc ccg ctt cca cct cca aag tcc cct cct gtg cct ccg<br>Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro Val Pro Pro<br>1075 1080 1085      | 5247 |
| cct cgg aag aag cgg acg gtg gtc ctc act gaa tca acc cta tct act<br>Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr Leu Ser Thr<br>1090 1095 1100      | 5295 |
| gcc ttg gcc gag ctc gcc acc aga agc ttt ggc agc tcc tca act tcc<br>Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser Ser Thr Ser<br>1105 1110 1115      | 5343 |
| ggc att acg ggc gac aat acg aca aca tcc tct gag ccc gcc cct tct<br>Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser<br>1120 1125 1130      | 5391 |
| ggc tgc ccc ccc gac tcc gac gct gag tcc tat tcc tcc atg ccc ccc<br>Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser Met Pro Pro<br>1135 1140 1145 1150 | 5439 |
| ctg gag ggg gag cct ggg gat ccg gat ctt agc gac ggg tca tgg tca<br>Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser<br>1155 1160 1165      | 5487 |
| acg gtc agt agt gag gcc aac gcg gag gat gtc gtg tgc tgc tca atg<br>Thr Val Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys Cys Ser Met<br>1170 1175 1180      | 5535 |
| tct tac tct tgg aca ggc gca ctc gtc acc ccg tgc gcc gcg gaa gaa<br>Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala Ala Glu Glu<br>1185 1190 1195      | 5583 |
| cag aaa ctg ccc atc aat gca cta agc aac tcg ttg cta cgt cac cac<br>Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His<br>1200 1205 1210      | 5631 |
| aat ttg gtg tat tcc acc acc tca cgc agt gct tgc caa agg cag aag<br>Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln Arg Gln Lys<br>1215 1220 1225 1230 | 5679 |
| aaa gtc aca ttt gac aga ctg caa gtt ctg gac agc cat tac cag gac<br>Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His Tyr Gln Asp<br>1235 1240 1245      | 5727 |
| gta ctc aag gag gtt aaa gca gcg gcg tca aaa gtg aag gct aac ttg<br>Val Leu Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys Ala Asn Leu<br>1250 1255 1260      | 5775 |
| cta tcc gta gag gaa gct tgc agc ctg acg ccc cca cac tca gcc aaa<br>Leu Ser Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys<br>1265 1270 1275      | 5823 |
| tcc aag ttt ggt tat ggg gca aaa gac gtc cgt tgc cat gcc aga aag<br>Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His Ala Arg Lys<br>1280 1285 1290      | 5871 |

|                                                                                    |      |
|------------------------------------------------------------------------------------|------|
| gcc gta acc cac atc aac tcc gtg tgg aaa gac ctt ctg gaa gac aat                    | 5919 |
| Ala Val Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn                    |      |
| 1295                      1300                      1305                      1310 |      |
| gta aca cca ata gac act acc atc atg gct aag aac gag gtt ttc tgc                    | 5967 |
| Val Thr Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys                    |      |
| 1315                      1320                      1325                           |      |
| gtt cag cct gag aag ggg ggt cgt aag cca gct cgt ctc atc gtg ttc                    | 6015 |
| Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe                    |      |
| 1330                      1335                      1340                           |      |
| ccc gat ctg ggc gtg cgc gtg tgc gaa aag atg gct ttg tac gac gtg                    | 6063 |
| Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val                    |      |
| 1345                      1350                      1355                           |      |
| gtt aca aag ctc ccc ttg gcc gtg atg gga agc tcc tac gga ttc caa                    | 6111 |
| Val Thr Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln                    |      |
| 1360                      1365                      1370                           |      |
| tac tca cca gga cag cgg gtt gaa ttc ctc gtg caa gcg tgg aag tcc                    | 6159 |
| Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser                    |      |
| 1375                      1380                      1385                      1390 |      |
| aag aaa acc cca atg ggg ttc tgc tat gat acc cgc tgc ttt gac tcc                    | 6207 |
| Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser                    |      |
| 1395                      1400                      1405                           |      |
| aca gtc act gag agc gac atc cgt acg gag gag gca atc tac caa tgt                    | 6255 |
| Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys                    |      |
| 1410                      1415                      1420                           |      |
| tgt gac ctc gac ccc caa gcc cgc gtg gcc atc aag tcc ctc acc gag                    | 6303 |
| Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu                    |      |
| 1425                      1430                      1435                           |      |
| agg ctt tat gtt ggg ggc cct ctt acc aat tca agg ggg gag aac tgc                    | 6351 |
| Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys                    |      |
| 1440                      1445                      1450                           |      |
| ggc tat cgc agg tgc cgc gcg agc ggc gta ctg aca act agc tgt ggt                    | 6399 |
| Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly                    |      |
| 1455                      1460                      1465                      1470 |      |
| aac acc ctc act tgc tac atc aag gcc cgg gca gcc tgt cga gcc gca                    | 6447 |
| Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala                    |      |
| 1475                      1480                      1485                           |      |
| ggg ctc cag gac tgc acc atg ctc gtg tgt ggc gac gac tta gtc gtt                    | 6495 |
| Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val                    |      |
| 1490                      1495                      1500                           |      |
| atc tgt gaa agc gcg ggg gtc cag gag gac gcg gcg agc ctg aga gcc                    | 6543 |
| Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser Leu Arg Ala                    |      |
| 1505                      1510                      1515                           |      |
| ttc acg gag gct atg acc agg tac tcc gcc ccc cct ggg gac ccc cca                    | 6591 |
| Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro                    |      |
| 1520                      1525                      1530                           |      |

9



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<211> 1771

<212> PRT

<213> Hepatitis C virus

<220>

<223> Description of Artificial Sequence: Hepatitis C pns345

<400> 2

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
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| Met | Ala | Ala | Tyr | Ala | Ala | Gln | Gly | Tyr | Lys | Val | Leu | Val | Leu | Asn | Pro |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Ser | Val | Ala | Ala | Thr | Leu | Gly | Phe | Gly | Ala | Tyr | Met | Ser | Lys | Ala | His |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Gly | Ile | Asp | Pro | Asn | Ile | Arg | Thr | Gly | Val | Arg | Thr | Ile | Thr | Thr | Gly |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Ser | Pro | Ile | Thr | Tyr | Ser | Thr | Tyr | Gly | Lys | Phe | Leu | Ala | Asp | Gly | Gly |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Cys | Ser | Gly | Gly | Ala | Tyr | Asp | Ile | Ile | Ile | Cys | Asp | Glu | Cys | His | Ser |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     | 80  |     |
| Thr | Asp | Ala | Thr | Ser | Ile | Leu | Gly | Ile | Gly | Thr | Val | Leu | Asp | Gln | Ala |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Glu | Thr | Ala | Gly | Ala | Arg | Leu | Val | Val | Leu | Ala | Thr | Ala | Thr | Pro | Pro |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| Gly | Ser | Val | Thr | Val | Pro | His | Pro | Asn | Ile | Glu | Glu | Val | Ala | Leu | Ser |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| Thr | Thr | Gly | Glu | Ile | Pro | Phe | Tyr | Gly | Lys | Ala | Ile | Pro | Leu | Glu | Val |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| Ile | Lys | Gly | Gly | Arg | His | Leu | Ile | Phe | Cys | His | Ser | Lys | Lys | Lys | Cys |
| 145 |     |     |     |     | 150 |     |     |     | 155 |     |     |     |     | 160 |     |
| Asp | Glu | Leu | Ala | Ala | Lys | Leu | Val | Ala | Leu | Gly | Ile | Asn | Ala | Val | Ala |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|-----|
|     |     |     |     | 165 |     |     |     |     |     | 170 |     |     |     |     |     |  | 175 |
| Tyr | Tyr | Arg | Gly | Leu | Asp | Val | Ser | Val | Ile | Pro | Thr | Ser | Gly | Asp | Val |  |     |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |     |
| Val | Val | Val | Ala | Thr | Asp | Ala | Leu | Met | Thr | Gly | Tyr | Thr | Gly | Asp | Phe |  |     |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |     |
| Asp | Ser | Val | Ile | Asp | Cys | Asn | Thr | Cys | Val | Thr | Gln | Thr | Val | Asp | Phe |  |     |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |     |
| Ser | Leu | Asp | Pro | Thr | Phe | Thr | Ile | Glu | Thr | Ile | Thr | Leu | Pro | Gln | Asp |  |     |
| 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |     |
| Ala | Val | Ser | Arg | Thr | Gln | Arg | Arg | Gly | Arg | Thr | Gly | Arg | Gly | Lys | Pro |  |     |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |  |     |
| Gly | Ile | Tyr | Arg | Phe | Val | Ala | Pro | Gly | Glu | Arg | Pro | Ser | Gly | Met | Phe |  |     |
|     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |     |
| Asp | Ser | Ser | Val | Leu | Cys | Glu | Cys | Tyr | Asp | Ala | Gly | Cys | Ala | Trp | Tyr |  |     |
|     | 275 |     |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |     |
| Glu | Leu | Thr | Pro | Ala | Glu | Thr | Thr | Val | Arg | Leu | Arg | Ala | Tyr | Met | Asn |  |     |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |     |
| Thr | Pro | Gly | Leu | Pro | Val | Cys | Gln | Asp | His | Leu | Glu | Phe | Trp | Glu | Gly |  |     |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |     |
| Val | Phe | Thr | Gly | Leu | Thr | His | Ile | Asp | Ala | His | Phe | Leu | Ser | Gln | Thr |  |     |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |     |
| Lys | Gln | Ser | Gly | Glu | Asn | Leu | Pro | Tyr | Leu | Val | Ala | Tyr | Gln | Ala | Thr |  |     |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |     |
| Val | Cys | Ala | Arg | Ala | Gln | Ala | Pro | Pro | Pro | Ser | Trp | Asp | Gln | Met | Trp |  |     |
|     | 355 |     |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |     |
| Lys | Cys | Leu | Ile | Arg | Leu | Lys | Pro | Thr | Leu | His | Gly | Pro | Thr | Pro | Leu |  |     |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |     |
| Leu | Tyr | Arg | Leu | Gly | Ala | Val | Gln | Asn | Glu | Ile | Thr | Leu | Thr | His | Pro |  |     |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |     |
| Val | Thr | Lys | Tyr | Ile | Met | Thr | Cys | Met | Ser | Ala | Asp | Leu | Glu | Val | Val |  |     |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |  |     |
| Thr | Ser | Thr | Trp | Val | Leu | Val | Gly | Gly | Val | Leu | Ala | Ala | Leu | Ala | Ala |  |     |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |     |
| Tyr | Cys | Leu | Ser | Thr | Gly | Cys | Val | Val | Ile | Val | Gly | Arg | Val | Val | Leu |  |     |
|     | 435 |     |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |  |     |
| Ser | Gly | Lys | Pro | Ala | Ile | Ile | Pro | Asp | Arg | Glu | Val | Leu | Tyr | Arg | Glu |  |     |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |  |     |
| Phe | Asp | Glu | Met | Glu | Glu | Cys | Ser | Gln | His | Leu | Pro | Tyr | Ile | Glu | Gln |  |     |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |  |     |

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 Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Arg Val  
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14

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 Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His Tyr Gln Asp Val Leu  
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 1475 1480 1485  
 Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys  
 1490 1495 1500  
 Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser Leu Arg Ala Phe Thr  
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Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys
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His Ser Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp
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Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr
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Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala
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Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu
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|                                                                 |      |
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| 145 150 155                                                     |      |
| aag tgc gac gaa ctc gcc gca aag ctg gtc gca ttg ggc atc aat gcc | 2511 |
| Lys Cys Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala |      |
| 160 165 170                                                     |      |
| gtg gcc tac tac cgc ggt ctt gac gtg tcc gtc atc ccg acc agc ggc | 2559 |
| Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly |      |
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| Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly |      |
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| Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val |      |
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| gat ttc agc ctt gac cct acc ttc acc att gag aca atc acg ctc ccc | 2703 |
| Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro |      |
| 225 230 235                                                     |      |
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| Gln Asp Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly |      |
| 240 245 250                                                     |      |
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| Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly |      |
| 255 260 265 270                                                 |      |
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| Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala |      |
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| tgg tat gag ctc acg ccc gcc gag act aca gtt agg cta cga gcg tac | 2895 |
| Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr |      |
| 290 295 300                                                     |      |
| atg aac acc ccg ggg ctt ccc gtg tgc cag gac cat ctt gaa ttt tgg | 2943 |
| Met Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp |      |
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| Glu Gly Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser |      |
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| cag aca aag cag agt ggg gag aac ctt cct tac ctg gta gcg tac caa | 3039 |
| Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln |      |
| 335 340 345 350                                                 |      |
| gcc acc gtg tgc gct agg gct caa gcc cct ccc cca tcg tgg gac cag | 3087 |
| Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln |      |
| 355 360 365                                                     |      |
| atg tgg aag tgt ttg att cgc ctc aag ccc acc ctc cat ggg cca aca | 3135 |
| Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr |      |
| 370 375 380                                                     |      |

|                                                                 |      |
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| Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile Thr Leu Thr |      |
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| cac cca gtc acc aaa tac atc atg aca tgc atg tcg gcc gac ctg gag | 3231 |
| His Pro Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala Asp Leu Glu |      |
| 400 405 410                                                     |      |
| gtc gtc acg agc acc tgg gtg ctc gtt ggc ggc gtc ctg gct gct ttg | 3279 |
| Val Val Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu |      |
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| gcc gcg tat tgc ctg tca aca ggc tgc gtg gtc ata gtg gcc agg gtc | 3327 |
| Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val Gly Arg Val |      |
| 435 440 445                                                     |      |
| gtc ttg tcc ggg aag ccg gca atc ata cct gac agg gaa gtc ctc tac | 3375 |
| Val Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr |      |
| 450 455 460                                                     |      |
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| Arg Glu Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr Ile |      |
| 465 470 475                                                     |      |
| gag caa ggg atg atg ctc gcc gag cag ttc aag cag aag gcc ctc ggc | 3471 |
| Glu Gln Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly |      |
| 480 485 490                                                     |      |
| ctc ctg cag acc gcg tcc cgt cag gca gag gtt atc gcc cct gct gtc | 3519 |
| Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala Pro Ala Val |      |
| 495 500 505 510                                                 |      |
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| 515 520 525                                                     |      |
| aac ttc atc agt ggg ata caa tac ttg gcg ggc ttg tca acg ctg cct | 3615 |
| Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro |      |
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| Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ala Val Thr |      |
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| Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly |      |
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| Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe Val |      |
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| ggc gct ggc tta gct ggc gcc gcc atc ggc agt gtt gga ctg ggg aag | 3807 |
| Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly Lys |      |
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| Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala |      |
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|                                                                 |      |
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| Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu |      |
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| ggg gca gtc cag tgg atg aac cgg ctg ata gcc ttc gcc tcc cgg ggg | 4047 |
| Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly |      |
| 675 680 685                                                     |      |
| aac cat gtt tcc ccc acg cac tac gtg ccg gag agc gat gca gct gcc | 4095 |
| Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala |      |
| 690 695 700                                                     |      |
| cgc gtc act gcc ata ctc agc agc ctc act gta acc cag ctc ctg agg | 4143 |
| Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln Leu Leu Arg |      |
| 705 710 715                                                     |      |
| cga ctg cac cag tgg ata agc tcg gag tgt acc act cca tgc tcc ggt | 4191 |
| Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly |      |
| 720 725 730                                                     |      |
| tcc tgg cta agg gac atc tgg gac tgg ata tgc gag gtg ttg agc gac | 4239 |
| Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp |      |
| 735 740 745 750                                                 |      |
| ttt aag acc tgg cta aaa gct aag ctc atg cca cag ctg cct ggg atc | 4287 |
| Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile |      |
| 755 760 765                                                     |      |
| ccc ttt gtg tcc tgc cag cgc ggg tat aag ggg gtc tgg cga ggg gac | 4335 |
| Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp |      |
| 770 775 780                                                     |      |
| ggc atc atg cac act cgc tgc cac tgt gga gct gag atc act gga cat | 4383 |
| Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile Thr Gly His |      |
| 785 790 795                                                     |      |
| gtc aaa aac ggg acg atg agg atc gtc ggt cct agg acc tgc agg aac | 4431 |
| Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr Cys Arg Asn |      |
| 800 805 810                                                     |      |
| atg tgg agt ggg acc ttc ccc att aat gcc tac acc acg ggc ccc tgt | 4479 |
| Met Trp Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys |      |
| 815 820 825 830                                                 |      |
| acc ccc ctt cct gcg ccg aac tac acg ttc gcg cta tgg agg gtg tct | 4527 |
| Thr Pro Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp Arg Val Ser |      |
| 835 840 845                                                     |      |
| gca gag gaa tac gtg gag ata agg cag gtg ggg gac ttc cac tac gtg | 4575 |
| Ala Glu Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe His Tyr Val |      |
| 850 855 860                                                     |      |

|                                                                 |      |
|-----------------------------------------------------------------|------|
| acg ggt atg act act gac aat ctt aaa tgc ccg tgc cag gtc cca tcg | 4623 |
| Thr Gly Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln Val Pro Ser |      |
| 865 870 875                                                     |      |
| ccc gaa ttt ttc aca gaa ttg gac ggg gtg cgc cta cat agg ttt gcg | 4671 |
| Pro Glu Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His Arg Phe Ala |      |
| 880 885 890                                                     |      |
| ccc ccc tgc aag ccc ttg ctg cgg gag gag gta tca ttc aga gta gga | 4719 |
| Pro Pro Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe Arg Val Gly |      |
| 895 900 905 910                                                 |      |
| ctc cac gaa tac ccg gta ggg tgc caa tta cct tgc gag ccc gaa ccg | 4767 |
| Leu His Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro |      |
| 915 920 925                                                     |      |
| gac gtg gcc gtg ttg acg tcc atg ctc act gat ccc tcc cat ata aca | 4815 |
| Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr |      |
| 930 935 940                                                     |      |
| gca gag gcg gcc ggg cga agg ttg gcg agg gga tca ccc ccc tct gtg | 4863 |
| Ala Glu Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Val |      |
| 945 950 955                                                     |      |
| gcc agc tcc tcg gct agc cag cta tcc gct cca tct ctc aag gca act | 4911 |
| Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr |      |
| 960 965 970                                                     |      |
| tgc acc gct aac cat gac tcc cct gat gct gag ctc ata gag gcc aac | 4959 |
| Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile Glu Ala Asn |      |
| 975 980 985 990                                                 |      |
| ctc cta tgg agg cag gag atg ggc ggc aac atc acc agg gtt gag tca | 5007 |
| Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser |      |
| 995 1000 1005                                                   |      |
| gaa aac aaa gtg gtg att ctg gac tcc ttc gat ccg ctt gtg gcg gag | 5055 |
| Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu Val Ala Glu |      |
| 1010 1015 1020                                                  |      |
| gag gac gag ccg gag atc tcc gta ccc gca gaa atc ctg ccg aag tct | 5103 |
| Glu Asp Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu Arg Lys Ser |      |
| 1025 1030 1035                                                  |      |
| ccg aga ttc gcc cag gcc ctg ccc gtt tgg gcg ccg ccg gac tat aac | 5151 |
| Arg Arg Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro Asp Tyr Asn |      |
| 1040 1045 1050                                                  |      |
| ccc ccg cta gtg gag acg tgg aaa aag ccc gac tac gaa cca cct gtg | 5199 |
| Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu Pro Pro Val |      |
| 1055 1060 1065 1070                                             |      |
| gtc cat ggc tgc ccg ctt cca cct cca aag tcc cct cct gtg cct ccg | 5247 |
| Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro Val Pro Pro |      |
| 1075 1080 1085                                                  |      |
| cct ccg aag aag ccg acg gtg gtc ctc act gaa tca acc cta tct act | 5295 |
| Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr Leu Ser Thr |      |
| 1090 1095 1100                                                  |      |

|                                                                 |      |
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| gcc ttg gcc gag ctc gcc acc aga agc ttt ggc agc tcc tca act tcc | 5343 |
| Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser Ser Thr Ser |      |
| 1105 1110 1115                                                  |      |
| ggc att acg ggc gac aat acg aca aca tcc tct gag ccc gcc cct tct | 5391 |
| Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser |      |
| 1120 1125 1130                                                  |      |
| ggc tgc ccc ccc gac tcc gac gct gag tcc tat tcc tcc atg ccc ccc | 5439 |
| Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser Met Pro Pro |      |
| 1135 1140 1145 1150                                             |      |
| ctg gag ggg gag cct ggg gat ccg gat ctt agc gac ggg tca tgg tca | 5487 |
| Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser |      |
| 1155 1160 1165                                                  |      |
| acg gtc agt agt gag gcc aac gcg gag gat gtc gtg tgc tgc tca atg | 5535 |
| Thr Val Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys Cys Ser Met |      |
| 1170 1175 1180                                                  |      |
| tct tac tct tgg aca ggc gca ctc gtc acc ccg tgc gcc gcg gaa gaa | 5583 |
| Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala Ala Glu Glu |      |
| 1185 1190 1195                                                  |      |
| cag aaa ctg ccc atc aat gca cta agc aac tcg ttg cta cgt cac cac | 5631 |
| Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His |      |
| 1200 1205 1210                                                  |      |
| aat ttg gtg tat tcc acc acc tca cgc agt gct tgc caa agg cag aag | 5679 |
| Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln Arg Gln Lys |      |
| 1215 1220 1225 1230                                             |      |
| aaa gtc aca ttt gac aga ctg caa gtt ctg gac agc cat tac cag gac | 5727 |
| Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His Tyr Gln Asp |      |
| 1235 1240 1245                                                  |      |
| gta ctc aag gag gtt aaa gca gcg gcg tca aaa gtg aag gct aac ttg | 5775 |
| Val Leu Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys Ala Asn Leu |      |
| 1250 1255 1260                                                  |      |
| cta tcc gta gag gaa gct tgc agc ctg acg ccc cca cac tca gcc aaa | 5823 |
| Leu Ser Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys |      |
| 1265 1270 1275                                                  |      |
| tcc aag ttt ggt tat ggg gca aaa gac gtc cgt tgc cat gcc aga aag | 5871 |
| Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His Ala Arg Lys |      |
| 1280 1285 1290                                                  |      |
| gcc gta acc cac atc aac tcc gtg tgg aaa gac ctt ctg gaa gac aat | 5919 |
| Ala Val Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn |      |
| 1295 1300 1305 1310                                             |      |
| gta aca cca ata gac act acc atc atg gct aag aac gag gtt ttc tgc | 5967 |
| Val Thr Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys |      |
| 1315 1320 1325                                                  |      |
| gtt cag cct gag aag ggg ggt cgt aag cca gct cgt ctc atc gtg ttc | 6015 |
| Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe |      |
| 1330 1335 1340                                                  |      |

|                                                                                                                                                           |      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| ccc gat ctg ggc gtg cgc gtg tgc gaa aag atg gct ttg tac gac gtg<br>Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val<br>1345 1350 1355      | 6063 |
| gtt aca aag ctc ccc ttg gcc gtg atg gga agc tcc tac gga ttc caa<br>Val Thr Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln<br>1360 1365 1370      | 6111 |
| tac tca cca gga cag cgg gtt gaa ttc ctc gtg caa gcg tgg aag tcc<br>Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser<br>1375 1380 1385 1390 | 6159 |
| aag aaa acc cca atg ggg ttc tcg tat gat acc cgc tgc ttt gac tcc<br>Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser<br>1395 1400 1405      | 6207 |
| aca gtc act gag agc gac atc cgt acg gag gag gca atc tac caa tgt<br>Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys<br>1410 1415 1420      | 6255 |
| tgt gac ctc gac ccc caa gcc cgc gtg gcc atc aag tcc ctc acc gag<br>Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu<br>1425 1430 1435      | 6303 |
| agg ctt tat gtt ggg ggc cct ctt acc aat tca agg ggg gag aac tgc<br>Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys<br>1440 1445 1450      | 6351 |
| ggc tat cgc agg tgc cgc gcg agc ggc gta ctg aca act agc tgt ggt<br>Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly<br>1455 1460 1465 1470 | 6399 |
| aac acc ctc act tgc tac atc aag gcc cgg gca gcc tgt cga gcc gca<br>Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala<br>1475 1480 1485      | 6447 |
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| atc tgt gaa agc gcg ggg gtc cag gag gac gcg gcg agc ctg aga gcc<br>Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser Leu Arg Ala<br>1505 1510 1515      | 6543 |
| ttc acg gag gct atg acc agg tac tcc gcc ccc cct ggg gac ccc cca<br>Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro<br>1520 1525 1530      | 6591 |
| caa cca gaa tac gac ttg gag ctc ata aca tca tgc tcc tcc aac gtg<br>Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val<br>1535 1540 1545 1550 | 6639 |
| tca gtc gcc cac gac ggc gct gga aag agg gtc tac tac ctc acc cgt<br>Ser Val Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr Leu Thr Arg<br>1555 1560 1565      | 6687 |
| gac cct aca acc ccc ctc gcg aga gct gcg tgg gag aca gca aga cac<br>Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His<br>1570 1575 1580      | 6735 |

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             20                    25                    30  
 Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly  
             35                    40                    45  
 Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly  
             50                    55                    60  
 Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser  
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 Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala  
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 Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro  
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 Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val  
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 Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe  
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 Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro

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Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val  
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 Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe Arg Val Gly Leu His  
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 Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser Gly Cys  
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 Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu  
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 Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val  
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 Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys Cys Ser Met Ser Tyr  
 1170 1175 1180  
 Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala Ala Glu Glu Gln Lys  
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Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu  
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 Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys  
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 1460 1465 1470  
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 Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr  
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 Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val  
 1730 1735 1740  
 Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys Leu Leu Leu Leu Ala  
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 Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg  
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&lt;210&gt; 5

&lt;211&gt; 4282

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: pCMVII

&lt;400&gt; 5

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 cgtatcacga ggccctttcg tc 4282

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<211> 6299

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: pNS34a

<220>

<221> CDS

<222> (1990)..(4047)

<400> 6

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 tggcgggtgt cggggtggc ttaactatgc ggcacagag cagattgtac tgagagtga 180  
 ccatatgaag ctttttgcaa aagcctaggc ctccaaaaaa gcctcctcac tacttctgga 240  
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 cgttgatatct atatcataat atgtacattt atattggctc atgtccaata tgaccgccat 420  
 gttgacattg attattgact agttattaat agtaatcaat tacgggggtca ttagttcata 480  
 gccatatat ggagttccgc gttacataac ttacggtaaa tggcccgct ggctgaccgc 540  
 ccaacgaccc ccgccattg acgtcaataa tgacgtatgt tcccatagta acgccaatag 600  
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 atcaagtgtg tcatatgcca agtccgcccc ctattgacgt caatgacggt aaatggcccc 720

cctggcatta tgcccagtac atgaccttac gggactttcc tacttggcag tacatctacg 780  
 tattagtcac cgctattacc atggtgatgc ggttttggca gtacaccaat gggcgtggat 840  
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 Met Ala Pro Ile Thr Ala Tyr Ala Gln Gln Thr Arg Gly Leu

1

5

10

cta ggg tgc ata atc acc agc cta act ggc cgg gac aaa aac caa gtg 2079  
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 15 20 25 30

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 Glu Gly Glu Val Gln Ile Val Ser Thr Ala Ala Gln Thr Phe Leu Ala  
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acg tgc atc aat ggg gtg tgc tgg act gtc tac cac ggg gcc gga acg 2175  
 Thr Cys Ile Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Thr  
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agg acc atc gcg tca ccc aag ggt cct gtc atc cag atg tat acc aat 2223

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| Arg | Thr | Ile | Ala | Ser | Pro | Lys | Gly | Pro | Val | Ile | Gln | Met | Tyr | Thr | Asn |      |
|     |     | 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |      |
| gta | gac | caa | gac | ctt | gtg | ggc | tgg | ccc | gct | tcg | caa | ggt | acc | cgc | tca | 2271 |
| Val | Asp | Gln | Asp | Leu | Val | Gly | Trp | Pro | Ala | Ser | Gln | Gly | Thr | Arg | Ser |      |
|     | 80  |     |     |     |     | 85  |     |     |     | 90  |     |     |     |     |     |      |
| ttg | aca | ccc | tgc | act | tgc | ggc | tcc | tcg | gac | ctt | tac | ctg | gtc | acg | agg | 2319 |
| Leu | Thr | Pro | Cys | Thr | Cys | Gly | Ser | Ser | Asp | Leu | Tyr | Leu | Val | Thr | Arg |      |
|     | 95  |     |     |     | 100 |     |     |     | 105 |     |     |     |     | 110 |     |      |
| cac | gcc | gat | gtc | att | ccc | gtg | cgc | cgg | cgg | ggt | gat | agc | agg | ggc | agc | 2367 |
| His | Ala | Asp | Val | Ile | Pro | Val | Arg | Arg | Arg | Gly | Asp | Ser | Arg | Gly | Ser |      |
|     |     |     | 115 |     |     |     |     | 120 |     |     |     |     |     | 125 |     |      |
| ctg | ctg | tcg | ccc | cgg | ccc | att | tcc | tac | ttg | aaa | ggc | tcc | tcg | ggg | ggt | 2415 |
| Leu | Leu | Ser | Pro | Arg | Pro | Ile | Ser | Tyr | Leu | Lys | Gly | Ser | Ser | Gly | Gly |      |
|     |     |     | 130 |     |     |     | 135 |     |     |     |     |     | 140 |     |     |      |
| ccg | ctg | ttg | tgc | ccc | gcg | ggg | cac | gcc | gtg | ggc | ata | ttt | agg | gcc | gcg | 2463 |
| Pro | Leu | Leu | Cys | Pro | Ala | Gly | His | Ala | Val | Gly | Ile | Phe | Arg | Ala | Ala |      |
|     | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     |      |
| gtg | tgc | acc | cgt | gga | gtg | gct | aag | gcg | gtg | gac | ttt | atc | cct | gtg | gag | 2511 |
| Val | Cys | Thr | Arg | Gly | Val | Ala | Lys | Ala | Val | Asp | Phe | Ile | Pro | Val | Glu |      |
|     | 160 |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     |     |      |
| aac | cta | gag | aca | acc | atg | agg | tcc | ccg | gtg | ttc | acg | gat | aac | tcc | tct | 2559 |
| Asn | Leu | Glu | Thr | Thr | Met | Arg | Ser | Pro | Val | Phe | Thr | Asp | Asn | Ser | Ser |      |
|     | 175 |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |      |
| cca | cca | gta | gtg | ccc | cag | agc | ttc | cag | gtg | gct | cac | ctc | cat | gct | ccc | 2607 |
| Pro | Pro | Val | Val | Pro | Gln | Ser | Phe | Gln | Val | Ala | His | Leu | His | Ala | Pro |      |
|     |     |     |     | 195 |     |     |     | 200 |     |     |     |     |     | 205 |     |      |
| aca | ggc | agc | ggc | aaa | agc | acc | aag | gtc | ccg | gct | gca | tat | gca | gct | cag | 2655 |
| Thr | Gly | Ser | Gly | Lys | Ser | Thr | Lys | Val | Pro | Ala | Ala | Tyr | Ala | Ala | Gln |      |
|     | 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |      |
| ggc | tat | aag | gtg | cta | gta | ctc | aac | ccc | tct | gtt | gct | gca | aca | ctg | ggc | 2703 |
| Gly | Tyr | Lys | Val | Leu | Val | Leu | Asn | Pro | Ser | Val | Ala | Ala | Ala | Thr | Leu | Gly  |
|     | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     |      |
| ttt | ggt | gct | tac | atg | tcc | aag | gct | cat | ggg | atc | gat | cct | aac | atc | agg | 2751 |
| Phe | Gly | Ala | Tyr | Met | Ser | Lys | Ala | His | Gly | Ile | Asp | Pro | Asn | Ile | Arg |      |
|     | 240 |     |     |     | 245 |     |     |     | 250 |     |     |     |     |     |     |      |
| acc | ggg | gtg | aga | aca | att | acc | act | ggc | agc | ccc | atc | acg | tac | tcc | acc | 2799 |
| Thr | Gly | Val | Arg | Thr | Ile | Thr | Thr | Gly | Ser | Pro | Ile | Thr | Tyr | Ser | Thr |      |
|     | 255 |     |     |     | 260 |     |     |     | 265 |     |     |     |     | 270 |     |      |
| tac | ggc | aag | ttc | ctt | gcc | gac | ggc | ggg | tgc | tcg | ggg | ggc | gct | tat | gac | 2847 |
| Tyr | Gly | Lys | Phe | Leu | Ala | Asp | Gly | Gly | Cys | Ser | Gly | Gly | Ala | Tyr | Asp |      |
|     |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |      |
| ata | ata | att | tgt | gac | gag | tgc | cac | tcc | acg | gat | gcc | aca | tcc | atc | ttg | 2895 |
| Ile | Ile | Ile | Cys | Asp | Glu | Cys | His | Ser | Thr | Asp | Ala | Thr | Ser | Ile | Leu |      |
|     |     |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |      |

|                                                                 |      |
|-----------------------------------------------------------------|------|
| ggc att ggc act gtc ctt gac caa gca gag act gcg ggg gcg aga ctg | 2943 |
| Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu |      |
| 305 310 315                                                     |      |
| ggt gtg ctc gcc acc gcc acc cct ccg ggc tcc gtc act gtg ccc cat | 2991 |
| Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His |      |
| 320 325 330                                                     |      |
| ccc aac atc gag gag gtt gct ctg tcc acc acc gga gag atc cct ttt | 3039 |
| Pro Asn Ile Glu Glu Val Ala Leu Ser Thr Thr Gly Glu Ile Pro Phe |      |
| 335 340 345 350                                                 |      |
| tac ggc aag gct atc ccc ctc gaa gta atc aag ggg ggg aga cat ctc | 3087 |
| Tyr Gly Lys Ala Ile Pro Leu Glu Val Ile Lys Gly Gly Arg His Leu |      |
| 355 360 365                                                     |      |
| atc ttc tgt cat tca aag aag aag tgc gac gaa ctc gcc gca aag ctg | 3135 |
| Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu |      |
| 370 375 380                                                     |      |
| gtc gca ttg ggc atc aat gcc gtg gcc tac tac cgc ggt ctt gac gtg | 3183 |
| Val Ala Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val |      |
| 385 390 395                                                     |      |
| tcc gtc atc ccg acc agc ggc gat gtt gtc gtc gtg gca acc gat gcc | 3231 |
| Ser Val Ile Pro Thr Ser Gly Asp Val Val Val Ala Thr Asp Ala     |      |
| 400 405 410                                                     |      |
| ctc atg acc ggc tat acc ggc gac ttc gac tcg gtg ata gac tgc aat | 3279 |
| Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn |      |
| 415 420 425 430                                                 |      |
| acg tgt gtc acc cag aca gtc gat ttc agc ctt gac cct acc ttc acc | 3327 |
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| 435 440 445                                                     |      |
| att gag aca atc acg ctc ccc caa gat gct gtc tcc cgc act caa cgt | 3375 |
| Ile Glu Thr Ile Thr Leu Pro Gln Asp Ala Val Ser Arg Thr Gln Arg |      |
| 450 455 460                                                     |      |
| cgg ggc agg act ggc agg ggg aag cca ggc atc tac aga ttt gtg gca | 3423 |
| Arg Gly Arg Thr Gly Arg Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala |      |
| 465 470 475                                                     |      |
| ccg ggg gag cgc ccc tcc ggc atg ttc gac tcg tcc gtc ctc tgt gag | 3471 |
| Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu |      |
| 480 485 490                                                     |      |
| tgc tat gac gca ggc tgt gct tgg tat gag ctc acg ccc gcc gag act | 3519 |
| Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr |      |
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| aca gtt agg cta cga gcg tac atg aac acc ccg ggg ctt ccc gtg tgc | 3567 |
| Thr Val Arg Leu Arg Ala Tyr Met Asn Thr Pro Gly Leu Pro Val Cys |      |
| 515 520 525                                                     |      |
| cag gac cat ctt gaa ttt tgg gag ggc gtc ttt aca ggc ctc act cat | 3615 |
| Gln Asp His Leu Glu Phe Trp Glu Gly Val Phe Thr Gly Leu Thr His |      |
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Ser Pro Arg Pro Ile Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu
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Leu Cys Pro Ala Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys
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tcgttccagt caggaatgtt ccacgtgaag ctatcttcca gcaaagtctc cacttcttca 11820



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|-----------------------------------------------------------------|-------|
| Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn |       |
| 110 115 120                                                     |       |
| atc gag gag gtt gct ctg tcc acc acc gga gag atc cct ttt tac ggc | 13155 |
| Ile Glu Glu Val Ala Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr Gly |       |
| 125 130 135                                                     |       |
| aag gct atc ccc ctc gaa gta atc aag ggg ggg aga cat ctc atc ttc | 13203 |
| Lys Ala Ile Pro Leu Glu Val Ile Lys Gly Gly Arg His Leu Ile Phe |       |
| 140 145 150                                                     |       |
| tgt cat tca aag aag aag tgc gac gaa ctc gcc gca aag ctg gtc gca | 13251 |
| Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Val Ala |       |
| 155 160 165                                                     |       |
| ttg ggc atc aat gcc gtg gcc tac tac cgc ggt ctt gac gtg tcc gtc | 13299 |
| Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val |       |
| 170 175 180 185                                                 |       |
| atc ccg acc agc ggc gat gtt gtc gtc gtg gca acc gat gcc ctc atg | 13347 |
| Ile Pro Thr Ser Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met |       |
| 190 195 200                                                     |       |
| acc ggc tat acc ggc gac ttc gac tcg gtg ata gac tgc aat acg tgt | 13395 |
| Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys |       |
| 205 210 215                                                     |       |
| gtc acc cag aca gtc gat ttc agc ctt gac cct acc ttc acc att gag | 13443 |
| Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu |       |
| 220 225 230                                                     |       |
| aca atc acg ctc ccc caa gat gct gtc tcc cgc act caa cgt cgg ggc | 13491 |
| Thr Ile Thr Leu Pro Gln Asp Ala Val Ser Arg Thr Gln Arg Arg Gly |       |
| 235 240 245                                                     |       |
| agg act ggc agg ggg aag cca ggc atc tac aga ttt gtg gca ccg ggg | 13539 |
| Arg Thr Gly Arg Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro Gly |       |
| 250 255 260 265                                                 |       |
| gag cgc ccc tcc ggc atg ttc gac tcg tcc gtc ctc tgt gag tgc tat | 13587 |
| Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr |       |
| 270 275 280                                                     |       |
| gac gca ggc tgt gct tgg tat gag ctc acg ccc gcc gag act aca gtt | 13635 |
| Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr Val |       |
| 285 290 295                                                     |       |
| agg cta cga gcg tac atg aac acc ccg ggg ctt ccc gtg tgc cag gac | 13683 |
| Arg Leu Arg Ala Tyr Met Asn Thr Pro Gly Leu Pro Val Cys Gln Asp |       |
| 300 305 310                                                     |       |
| cat ctt gaa ttt tgg gag ggc gtc ttt aca ggc ctc act cat ata gat | 13731 |
| His Leu Glu Phe Trp Glu Gly Val Phe Thr Gly Leu Thr His Ile Asp |       |
| 315 320 325                                                     |       |
| gcc cac ttt cta tcc cag aca aag cag agt ggg gag aac ctt cct tac | 13779 |
| Ala His Phe Leu Ser Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro Tyr |       |
| 330 335 340 345                                                 |       |

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|-----------------------------------------------------------------|-------|
| ctg gta gcg tac caa gcc acc gtg tgc gct agg gct caa gcc cct ccc | 13827 |
| Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro |       |
| 350 355 360                                                     |       |
| cca tcg tgg gac cag atg tgg aag tgt ttg att cgc ctc aag ccc acc | 13875 |
| Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr |       |
| 365 370 375                                                     |       |
| ctc cat ggg cca aca ccc ctg cta tac aga ctg ggc gct gtt cag aat | 13923 |
| Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn |       |
| 380 385 390                                                     |       |
| gaa atc acc ctg acg cac cca gtc acc aaa tac atc atg aca tgc atg | 13971 |
| Glu Ile Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met Thr Cys Met |       |
| 395 400 405                                                     |       |
| tcg gcc gac ctg gag gtc gtc acg agc acc tgg gtg ctc gtt ggc ggc | 14019 |
| Ser Ala Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu Val Gly Gly |       |
| 410 415 420 425                                                 |       |
| gtc ctg gct gct ttg gcc gcg tat tgc ctg tca aca ggc tgc gtg gtc | 14067 |
| Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val Val |       |
| 430 435 440                                                     |       |
| ata gtg ggc agg gtc gtc ttg tcc ggg aag ccg gca atc ata cct gac | 14115 |
| Ile Val Gly Arg Val Val Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp |       |
| 445 450 455                                                     |       |
| agg gaa gtc ctc tac cga gag ttc gat gag atg gaa gag tgc tct cag | 14163 |
| Arg Glu Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Glu Cys Ser Gln |       |
| 460 465 470                                                     |       |
| cac tta ccg tac atc gag caa ggg atg atg ctc gcc gag cag ttc aag | 14211 |
| His Leu Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe Lys |       |
| 475 480 485                                                     |       |
| cag aag gcc ctc ggc ctc ctg cag acc gcg tcc cgt cag gca gag gtt | 14259 |
| Gln Lys Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu Val |       |
| 490 495 500 505                                                 |       |
| atc gcc cct gct gtc cag acc aac tgg caa aaa ctc gag acc ttc tgg | 14307 |
| Ile Ala Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe Trp |       |
| 510 515 520                                                     |       |
| gcg aag cat atg tgg aac ttc atc agt ggg ata caa tac ttg gcg ggc | 14355 |
| Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly |       |
| 525 530 535                                                     |       |
| ttg tca acg ctg cct ggt aac ccc gcc att gct tca ttg atg gct ttt | 14403 |
| Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe |       |
| 540 545 550                                                     |       |
| aca gct gct gtc acc agc cca cta acc act agc caa acc ctc ctc ttc | 14451 |
| Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu Phe |       |
| 555 560 565                                                     |       |
| aac ata ttg ggg ggg tgg gtg gct gcc cag ctc gcc gcc ccc ggt gcc | 14499 |
| Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala |       |
| 570 575 580 585                                                 |       |

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|-----------------------------------------------------------------|-------|
| gct act gcc ttt gtg ggc gct ggc tta gct ggc gcc gcc atc ggc agt | 14547 |
| Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser |       |
| 590 595 600                                                     |       |
| gtt gga ctg ggg aag gtc ctc ata gac atc ctt gca ggg tat ggc gcg | 14595 |
| Val Gly Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala |       |
| 605 610 615                                                     |       |
| ggc gtg gcg gga gct ctt gtg gca ttc aag atc atg agc ggt gag gtc | 14643 |
| Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu Val |       |
| 620 625 630                                                     |       |
| ccc tcc acg gag gac ctg gtc aat cta ctg ccc gcc atc ctc tcg ccc | 14691 |
| Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro |       |
| 635 640 645                                                     |       |
| gga gcc ctc gta gtc ggc gtg gtc tgt gca gca ata ctg cgc cgg cac | 14739 |
| Gly Ala Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His |       |
| 650 655 660 665                                                 |       |
| gtt ggc ccg ggc gag ggg gca gtg cag tgg atg aac cgg ctg ata gcc | 14787 |
| Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala |       |
| 670 675 680                                                     |       |
| ttc gcc tcc cgg ggg aac cat gtt tcc ccc acg cac tac gtg ccg gag | 14835 |
| Phe Ala Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro Glu |       |
| 685 690 695                                                     |       |
| agc gat gca gct gcc cgc gtc act gcc ata ctc agc agc ctc act gta | 14883 |
| Ser Asp Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val |       |
| 700 705 710                                                     |       |
| acc cag ctc ctg agg cga ctg cac cag tgg ata agc tcg gag tgt acc | 14931 |
| Thr Gln Leu Leu Arg Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr |       |
| 715 720 725                                                     |       |
| act cca tgc tcc ggt tcc tgg cta agg gac atc tgg gac tgg ata tgc | 14979 |
| Thr Pro Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys |       |
| 730 735 740 745                                                 |       |
| gag gtg ttg agc gac ttt aag acc tgg cta aaa gct aag ctc atg cca | 15027 |
| Glu Val Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro |       |
| 750 755 760                                                     |       |
| cag ctg cct ggg atc ccc ttt gtg tcc tgc cag cgc ggg tat aag ggg | 15075 |
| Gln Leu Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly |       |
| 765 770 775                                                     |       |
| gtc tgg cga ggg gac ggc atc atg cac act cgc tgc cac tgt gga gct | 15123 |
| Val Trp Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala |       |
| 780 785 790                                                     |       |
| gag atc act gga cat gtc aaa aac ggg acg atg agg atc gtc ggt cct | 15171 |
| Glu Ile Thr Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro |       |
| 795 800 805                                                     |       |
| agg acc tgc agg aac atg tgg agt ggg acc ttc ccc att aat gcc tac | 15219 |
| Arg Thr Cys Arg Asn Met Trp Ser Gly Thr Phe Pro Ile Asn Ala Tyr |       |
| 810 815 820 825                                                 |       |

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|-----------------------------------------------------------------|-------|
| acc acg ggc ccc tgt acc ccc ctt cct gcg ccg aac tac acg ttc gcg | 15267 |
| Thr Thr Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Thr Phe Ala |       |
| 830 835 840                                                     |       |
| cta tgg agg gtg tct gca gag gaa tac gtg gag ata agg cag gtg ggg | 15315 |
| Leu Trp Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Gln Val Gly |       |
| 845 850 855                                                     |       |
| gac ttc cac tac gtg acg ggt atg act act gac aat ctt aaa tgc ccg | 15363 |
| Asp Phe His Tyr Val Thr Gly Met Thr Thr Asp Asn Leu Lys Cys Pro |       |
| 860 865 870                                                     |       |
| tgc cag gtc cca tgc ccc gaa ttt ttc aca gaa ttg gac ggg gtg cgc | 15411 |
| Cys Gln Val Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val Arg |       |
| 875 880 885                                                     |       |
| cta cat agg ttt gcg ccc ccc tgc aag ccc ttg ctg cgg gag gag gta | 15459 |
| Leu His Arg Phe Ala Pro Cys Lys Pro Leu Leu Arg Glu Glu Val     |       |
| 890 895 900 905                                                 |       |
| tca ttc aga gta gga ctc cac gaa tac ccg gta ggg tgc caa tta cct | 15507 |
| Ser Phe Arg Val Gly Leu His Glu Tyr Pro Val Gly Ser Gln Leu Pro |       |
| 910 915 920                                                     |       |
| tgc gag ccc gaa ccg gac gtg gcc gtg ttg acg tcc atg ctc act gat | 15555 |
| Cys Glu Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp |       |
| 925 930 935                                                     |       |
| ccc tcc cat ata aca gca gag gcg gcc ggg cga agg ttg gcg agg gga | 15603 |
| Pro Ser His Ile Thr Ala Glu Ala Ala Gly Arg Arg Leu Ala Arg Gly |       |
| 940 945 950                                                     |       |
| tca ccc ccc tct gtg gcc agc tcc tgc gct agc cag cta tcc gct cca | 15651 |
| Ser Pro Pro Ser Val Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro |       |
| 955 960 965                                                     |       |
| tct ctc aag gca act tgc acc gct aac cat gac tcc cct gat gct gag | 15699 |
| Ser Leu Lys Ala Thr Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu |       |
| 970 975 980 985                                                 |       |
| ctc ata gag gcc aac ctc cta tgg agg cag gag atg ggc ggc aac atc | 15747 |
| Leu Ile Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile |       |
| 990 995 1000                                                    |       |
| acc agg gtt gag tca gaa aac aaa gtg gtg att ctg gac tcc ttc gat | 15795 |
| Thr Arg Val Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp |       |
| 1005 1010 1015                                                  |       |
| ccg ctt gtg gcg gag gag gac gag ccg gag atc tcc gta ccc gca gaa | 15843 |
| Pro Leu Val Ala Glu Glu Asp Glu Arg Glu Ile Ser Val Pro Ala Glu |       |
| 1020 1025 1030                                                  |       |
| atc ctg ccg aag tct ccg aga ttc gcc cag gcc ctg ccc gtt tgg gcg | 15891 |
| Ile Leu Arg Lys Ser Arg Arg Phe Ala Gln Ala Leu Pro Val Trp Ala |       |
| 1035 1040 1045                                                  |       |
| cgg ccg gac tat aac ccc ccg cta gtg gag acg tgg aaa aag ccc gac | 15939 |
| Arg Pro Asp Tyr Asn Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp |       |
| 1050 1055 1060 1065                                             |       |

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|-----------------------------------------------------------------|-------|
| tac gaa cca cct gtg gtc cat ggc tgc ccg ctt cca cct cca aag tcc | 15987 |
| Tyr Glu Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser |       |
| 1070 1075 1080                                                  |       |
| cct cct gtg cct ccg cct cgg aag aag cgg acg gtg gtc ctc act gaa | 16035 |
| Pro Pro Val Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu |       |
| 1085 1090 1095                                                  |       |
| tca acc cta tct act gcc ttg gcc gag ctc gcc acc aga agc ttt ggc | 16083 |
| Ser Thr Leu Ser Thr Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly |       |
| 1100 1105 1110                                                  |       |
| agc tcc tca act tcc ggc att acg ggc gac aat acg aca aca tcc tct | 16131 |
| Ser Ser Ser Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser |       |
| 1115 1120 1125                                                  |       |
| gag ccc gcc cct tct ggc tgc ccc ccc gac tcc gac gct gag tcc tat | 16179 |
| Glu Pro Ala Pro Ser Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr |       |
| 1130 1135 1140 1145                                             |       |
| tcc tcc atg ccc ccc ctg gag ggg gag cct ggg gat ccg gat ctt agc | 16227 |
| Ser Ser Met Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser |       |
| 1150 1155 1160                                                  |       |
| gac ggg tca tgg tca acg gtc agt agt gag gcc aac gcg gag gat gtc | 16275 |
| Asp Gly Ser Trp Ser Thr Val Ser Ser Glu Ala Asn Ala Glu Asp Val |       |
| 1165 1170 1175                                                  |       |
| gtg tgc tgc tca atg tct tac tct tgg aca ggc gca ctc gtc acc ccg | 16323 |
| Val Cys Cys Ser Met Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr Pro |       |
| 1180 1185 1190                                                  |       |
| tgc gcc gcg gaa gaa cag aaa ctg ccc atc aat gca cta agc aac tcg | 16371 |
| Cys Ala Ala Glu Glu Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser |       |
| 1195 1200 1205                                                  |       |
| ttg cta cgt cac cac aat ttg gtg tat tcc acc acc tca cgc agt gct | 16419 |
| Leu Leu Arg His His Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser Ala |       |
| 1210 1215 1220 1225                                             |       |
| tgc caa agg cag aag aaa gtc aca ttt gac aga ctg caa gtt ctg gac | 16467 |
| Cys Gln Arg Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp |       |
| 1230 1235 1240                                                  |       |
| agc cat tac cag gac gta ctc aag gag gtt aaa gca gcg gcg tca aaa | 16515 |
| Ser His Tyr Gln Asp Val Leu Lys Glu Val Lys Ala Ala Ala Ser Lys |       |
| 1245 1250 1255                                                  |       |
| gtg aag gct aac ttg cta tcc gta gag gaa gct tgc agc ctg acg ccc | 16563 |
| Val Lys Ala Asn Leu Leu Ser Val Glu Glu Ala Cys Ser Leu Thr Pro |       |
| 1260 1265 1270                                                  |       |
| cca cac tca gcc aaa tcc aag ttt ggt tat ggg gca aaa gac gtc cgt | 16611 |
| Pro His Ser Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg |       |
| 1275 1280 1285                                                  |       |
| tgc cat gcc aga aag gcc gta acc cac atc aac tcc gtg tgg aaa gac | 16659 |
| Cys His Ala Arg Lys Ala Val Thr His Ile Asn Ser Val Trp Lys Asp |       |
| 1290 1295 1300 1305                                             |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| ctt ctg gaa gac aat gta aca cca ata gac act acc atc atg gct aag | 16707 |
| Leu Leu Glu Asp Asn Val Thr Pro Ile Asp Thr Thr Ile Met Ala Lys |       |
| 1310 1315 1320                                                  |       |
| aac gag gtt ttc tgc gtt cag cct gag aag ggg ggt cgt aag cca gct | 16755 |
| Asn Glu Val Phe Cys Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala |       |
| 1325 1330 1335                                                  |       |
| cgt ctc atc gtg ttc ccc gat ctg ggc gtg cgc gtg tgc gaa aag atg | 16803 |
| Arg Leu Ile Val Phe Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met |       |
| 1340 1345 1350                                                  |       |
| gct ttg tac gac gtg gtt aca aag ctc ccc ttg gcc gtg atg gga agc | 16851 |
| Ala Leu Tyr Asp Val Val Thr Lys Leu Pro Leu Ala Val Met Gly Ser |       |
| 1355 1360 1365                                                  |       |
| tcc tac gga ttc caa tac tca cca gga cag cgg gtt gaa ttc ctc gtg | 16899 |
| Ser Tyr Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val |       |
| 1370 1375 1380 1385                                             |       |
| caa gcg tgg aag tcc aag aaa acc cca atg ggg ttc tcg tat gat acc | 16947 |
| Gln Ala Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr |       |
| 1390 1395 1400                                                  |       |
| cgc tgc ttt gac tcc aca gtc act gag agc gac atc cgt acg gag gag | 16995 |
| Arg Cys Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu |       |
| 1405 1410 1415                                                  |       |
| gca atc tac caa tgt tgt gac ctc gac ccc caa gcc cgc gtg gcc atc | 17043 |
| Ala Ile Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile |       |
| 1420 1425 1430                                                  |       |
| aag tcc ctc acc gag agg ctt tat gtt ggg ggc cct ctt acc aat tca | 17091 |
| Lys Ser Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser |       |
| 1435 1440 1445                                                  |       |
| agg ggg gag aac tgc ggc tat cgc agg tgc cgc gcg agc ggc gta ctg | 17139 |
| Arg Gly Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu |       |
| 1450 1455 1460 1465                                             |       |
| aca act agc tgt ggt aac acc ctc act tgc tac atc aag gcc cgg gca | 17187 |
| Thr Thr Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala |       |
| 1470 1475 1480                                                  |       |
| gcc tgt cga gcc gca ggg ctc cag gac tgc acc atg ctc gtg tgt ggc | 17235 |
| Ala Cys Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly |       |
| 1485 1490 1495                                                  |       |
| gac gac tta gtc gtt atc tgt gaa agc gcg ggg gtc cag gag gac gcg | 17283 |
| Asp Asp Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala |       |
| 1500 1505 1510                                                  |       |
| gcg agc ctg aga gcc ttc acg gag gct atg acc agg tac tcc gcc ccc | 17331 |
| Ala Ser Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro |       |
| 1515 1520 1525                                                  |       |
| cct ggg gac ccc cca caa cca gaa tac gac ttg gag ctc ata aca tca | 17379 |
| Pro Gly Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser |       |
| 1530 1535 1540 1545                                             |       |

|                                                                                                                                                           |       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| tgc tcc tcc aac gtg tca gtc gcc cac gac ggc gct gga aag agg gtc<br>Cys Ser Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg Val<br>1550 1555 1560      | 17427 |
| tac tac ctc acc cgt gac cct aca acc ccc ctc gcg aga gct gcg tgg<br>Tyr Tyr Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp<br>1565 1570 1575      | 17475 |
| gag aca gca aga cac act cca gtc aat tcc tgg cta ggc aac ata atc<br>Glu Thr Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile<br>1580 1585 1590      | 17523 |
| atg ttt gcc ccc aca ctg tgg gcg agg atg ata ctg atg acc cat ttc<br>Met Phe Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe<br>1595 1600 1605      | 17571 |
| ttt agc gtc ctt ata gcc agg gac cag ctt gaa cag gcc ctc gat tgc<br>Phe Ser Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp Cys<br>1610 1615 1620 1625 | 17619 |
| gag atc tac ggg gcc tgc tac tcc ata gaa cca ctg gat cta cct cca<br>Glu Ile Tyr Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Pro<br>1630 1635 1640      | 17667 |
| atc att caa aga ctc cat ggc ctc agc gca ttt tca ctc cac agt tac<br>Ile Ile Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr<br>1645 1650 1655      | 17715 |
| tct cca ggt gaa atc aat agg gtg gcc gca tgc ctc aga aaa ctt ggg<br>Ser Pro Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly<br>1660 1665 1670      | 17763 |
| gta ccg ccc ttg cga gct tgg aga cac cgg gcc cgg agc gtc cgc gct<br>Val Pro Pro Leu Arg Ala Trp Arg His Arg Ala Arg Ser Val Arg Ala<br>1675 1680 1685      | 17811 |
| agg ctt ctg gcc aga gga ggc agg gct gcc ata tgt ggc aag tac ctc<br>Arg Leu Leu Ala Arg Gly Gly Arg Ala Ala Ile Cys Gly Lys Tyr Leu<br>1690 1695 1700 1705 | 17859 |
| ttc aac tgg gca gta aga aca aag ctc aaa ctc act cca ata gcg gcc<br>Phe Asn Trp Ala Val Arg Thr Lys Leu Lys Leu Thr Pro Ile Ala Ala<br>1710 1715 1720      | 17907 |
| gct ggc cag ctg gac ttg tcc ggc tgg ttc acg gct ggc tac agc ggg<br>Ala Gly Gln Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser Gly<br>1725 1730 1735      | 17955 |
| gga gac att tat cac agc gtg tct cat gcc cgg ccc cgc tgg atc tgg<br>Gly Asp Ile Tyr His Ser Val Ser His Ala Arg Pro Arg Trp Ile Trp<br>1740 1745 1750      | 18003 |
| ttt tgc cta ctc ctg ctt gct gca ggg gta ggc atc tac ctc ctc ccc<br>Phe Cys Leu Leu Leu Leu Ala Ala Gly Val Gly Ile Tyr Leu Leu Pro<br>1755 1760 1765      | 18051 |
| aac cga tgaaggttgg ggtaaacact ccggcctaaa aaaaaaaaaa aatctagaac<br>Asn Arg<br>1770                                                                         | 18107 |



ccgagtcgac tttgttccca ctgtactttt agctcgtaca aaatacaata tacttttcat 18167  
ttctccgtaa acaacatggt ttcccatgta atatcctttt ctatttttcg ttccggtacc 18227  
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taattttgct gcctgccata tttcaatttg ttataaattc ctataattta tcctattagt 18347  
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gttaagaata ctgggcaatt tcatgtttct tcaacactac atatgcgtat atataccaat 19787  
ctaagtctgt gtccttccct tcgttcttcc ttctgttcgg agattaccga atcaaaaaaa 19847  
tttcaaggaa accgaaatca aaaaaagaa taaaaaaaa atgatgaatt gaaaagctta 19907

tcgat

19912

&lt;210&gt; 9

&lt;211&gt; 1771

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: pd.deltaNS3NS5

&lt;400&gt; 9

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Met Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro
  1              5              10              15

Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His
      20              25              30

Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly
      35              40              45

Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly
      50              55              60

Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser
      65              70              75              80

Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala
      85              90              95

Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro
      100             105             110

Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser
      115             120             125

Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val
      130             135             140

Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys
      145             150             155             160

Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala
      165             170             175

Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val
      180             185             190

Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe
      195             200             205

Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe
      210             215             220

Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro Gln Asp
      225             230             235             240

Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro
      245             250             255

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Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly M t Phe  
 260 265 270  
 Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr  
 275 280 285  
 Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn  
 290 295 300  
 Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly  
 305 310 315 320  
 Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr  
 325 330 335  
 Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln Ala Thr  
 340 345 350  
 Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp  
 355 360 365  
 Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu  
 370 375 380  
 Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile Thr Leu Thr His Pro  
 385 390 395 400  
 Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala Asp Leu Glu Val Val  
 405 410 415  
 Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala  
 420 425 430  
 Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val Gly Arg Val Val Leu  
 435 440 445  
 Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu  
 450 455 460  
 Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln  
 465 470 475 480  
 Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu  
 485 490 495  
 Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala Pro Ala Val Gln Thr  
 500 505 510  
 Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys His Met Trp Asn Phe  
 515 520 525  
 Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn  
 530 535 540  
 Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro  
 545 550 555 560  
 Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val  
 565 570 575

Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala  
 580 585 590  
 Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu  
 595 600 605  
 Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val  
 610 615 620  
 Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val  
 625 630 635 640  
 Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val  
 645 650 655  
 Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala  
 660 665 670  
 Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His  
 675 680 685  
 Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val  
 690 695 700  
 Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln Leu Leu Arg Arg Leu  
 705 710 715 720  
 His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp  
 725 730 735  
 Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys  
 740 745 750  
 Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe  
 755 760 765  
 Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile  
 770 775 780  
 Met His Thr Arg Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys  
 785 790 795 800  
 Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr Cys Arg Asn Met Trp  
 805 810 815  
 Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro  
 820 825 830  
 Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp Arg Val Ser Ala Glu  
 835 840 845  
 Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe His Tyr Val Thr Gly  
 850 855 860  
 Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln Val Pro Ser Pro Glu  
 865 870 875 880  
 Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His Arg Phe Ala Pro Pro  
 885 890 895

Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe Arg Val Gly Leu His  
                   900                                  905                                  910  
 Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val  
                   915                                  920                                  925  
 Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu  
                   930                                  935                                  940  
 Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Val Ala Ser  
                   945                                  950                                  955                                  960  
 Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr  
                                   965                                  970                                  975  
 Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile Glu Ala Asn Leu Leu  
                                   980                                  985                                  990  
 Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn  
                   995                                  1000                                  1005  
 Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu Val Ala Glu Glu Asp  
                   1010                                  1015                                  1020  
 Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Arg Arg  
                   025                                  1030                                  1035                                  1040  
 Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro Asp Tyr Asn Pro Pro  
                                   1045                                  1050                                  1055  
 Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu Pro Pro Val Val His  
                   1060                                  1065                                  1070  
 Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro Val Pro Pro Pro Arg  
                   1075                                  1080                                  1085  
 Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr Leu Ser Thr Ala Leu  
                   1090                                  1095                                  1100  
 Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser Ser Thr Ser Gly Ile  
                   105                                  1110                                  1115                                  1120  
 Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser Gly Cys  
                                   1125                                  1130                                  1135  
 Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu  
                   1140                                  1145                                  1150  
 Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val  
                   1155                                  1160                                  1165  
 Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys Cys Ser Met Ser Tyr  
                   1170                                  1175                                  1180  
 Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala Ala Glu Glu Gln Lys  
                   185                                  1190                                  1195                                  1200  
 Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu  
                                   1205                                  1210                                  1215

Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln Arg Gln Lys Lys Val  
 1220 1225 1230  
 Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His Tyr Gln Asp Val Leu  
 1235 1240 1245  
 Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser  
 1250 1255 1260  
 Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys  
 265 1270 1275 1280  
 Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val  
 1285 1290 1295  
 Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn Val Thr  
 1300 1305 1310  
 Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln  
 1315 1320 1325  
 Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp  
 1330 1335 1340  
 Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr  
 345 1350 1355 1360  
 Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser  
 1365 1370 1375  
 Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys  
 1380 1385 1390  
 Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val  
 1395 1400 1405  
 Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp  
 1410 1415 1420  
 Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu  
 425 1430 1435 1440  
 Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr  
 1445 1450 1455  
 Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr  
 1460 1465 1470  
 Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu  
 1475 1480 1485  
 Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys  
 1490 1495 1500  
 Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser Leu Arg Ala Phe Thr  
 505 1510 1515 1520  
 Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Gln Pro  
 1525 1530 1535

Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val  
           1540                          1545                          1550  
 Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro  
           1555                          1560                          1565  
 Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro  
           1570                          1575                          1580  
 Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe Ala Pro Thr Leu Trp  
 585                          1590                          1595                          1600  
 Ala Arg Met Ile Leu Met Thr His Phe Phe Ser Val Leu Ile Ala Arg  
                           1605                          1610                          1615  
 Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile Tyr Gly Ala Cys Tyr  
           1620                          1625                          1630  
 Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu His Gly  
           1635                          1640                          1645  
 Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg  
           1650                          1655                          1660  
 Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Ala Trp  
 665                          1670                          1675                          1680  
 Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ala Arg Gly Gly  
                           1685                          1690                          1695  
 Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr  
           1700                          1705                          1710  
 Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly Gln Leu Asp Leu Ser  
           1715                          1720                          1725  
 Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val  
           1730                          1735                          1740  
 Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys Leu Leu Leu Leu Ala  
 745                          1750                          1755                          1760  
 Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg  
                           1765                          1770

&lt;210&gt; 10

&lt;211&gt; 19798

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence:

pd.deltaNS3NS5.pj

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (12679) .. (17991)

&lt;400&gt; 10

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cggatcaacg ttcttaatat cgctgaatct tccacaattg atgaaagtag ctaggaagag 180  
gaattggtat aaagtttttg tttttgtaa tctcgaagta tactcaaacg aatttagtat 240  
tttctcagtg atctcccaga tgctttcacc ctacttaga agtgctttaa gcattttttt 300  
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|                                                                 | 60 65 70 75     |                                             |            |            |            |       |
| gac gag tgc cac tcc acg gat gcc aca tcc atc ttg ggc att ggc act | 12951           |                                             |            |            |            |       |
| Asp Glu Cys His Ser Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr |                 |                                             |            |            |            |       |
|                                                                 | 80 85 90        |                                             |            |            |            |       |
| gtc ctt gac caa gca gag act gcg ggg gcg aga ctg gtt gtg ctc gcc | 12999           |                                             |            |            |            |       |
| Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala |                 |                                             |            |            |            |       |
|                                                                 | 95 100 105      |                                             |            |            |            |       |
| acc gcc acc cct ccg ggc tcc gtc act gtg ccc cat ccc aac atc gag | 13047           |                                             |            |            |            |       |
| Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu |                 |                                             |            |            |            |       |
|                                                                 | 110 115 120     |                                             |            |            |            |       |
| gag gtt gct ctg tcc acc acc gga gag atc cct ttt tac ggc aag gct | 13095           |                                             |            |            |            |       |
| Glu Val Ala Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala |                 |                                             |            |            |            |       |
|                                                                 | 125 130 135     |                                             |            |            |            |       |
| atc ccc ctc gaa gta atc aag ggg ggg aga cat ctc atc ttc tgt cat | 13143           |                                             |            |            |            |       |
| Ile Pro Leu Glu Val Ile Lys Gly Gly Arg His Leu Ile Phe Cys His |                 |                                             |            |            |            |       |
|                                                                 | 140 145 150 155 |                                             |            |            |            |       |
| tca aag aag aag tgc gac gaa ctc gcc gca aag ctg gtc gca ttg ggc | 13191           |                                             |            |            |            |       |
| Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly |                 |                                             |            |            |            |       |
|                                                                 | 160 165 170     |                                             |            |            |            |       |
| atc aat gcc gtg gcc tac tac cgc ggt ctt gac gtg tcc gtc atc ccg | 13239           |                                             |            |            |            |       |
| Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro |                 |                                             |            |            |            |       |
|                                                                 | 175 180 185     |                                             |            |            |            |       |
| acc agc ggc gat gtt gtc gtc gtg gca acc gat gcc ctc atg acc ggc | 13287           |                                             |            |            |            |       |
| Thr Ser Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly |                 |                                             |            |            |            |       |
|                                                                 | 190 195 200     |                                             |            |            |            |       |
| tat acc ggc gac ttc gac tcg gtg ata gac tgc aat acg tgt gtc acc | 13335           |                                             |            |            |            |       |
| Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr |                 |                                             |            |            |            |       |
|                                                                 | 205 210 215     |                                             |            |            |            |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| cag aca gtc gat ttc agc ctt gac cct acc ttc acc att gag aca atc | 13383 |
| Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile |       |
| 220 225 230 235                                                 |       |
| acg ctc ccc caa gat gct gtc tcc cgc act caa cgt cgg ggc agg act | 13431 |
| Thr Leu Pro Gln Asp Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr |       |
| 240 245 250                                                     |       |
| ggc agg ggg aag cca ggc atc tac aga ttt gtg gca ccg ggg gag cgc | 13479 |
| Gly Arg Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg |       |
| 255 260 265                                                     |       |
| ccc tcc ggc atg ttc gac tcg tcc gtc ctc tgt gag tgc tat gac gca | 13527 |
| Pro Ser Gly Met Phe Asp Ser Val Leu Cys Glu Cys Tyr Asp Ala     |       |
| 270 275 280                                                     |       |
| ggc tgt gct tgg tat gag ctc acg ccc gcc gag act aca gtt agg cta | 13575 |
| Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu |       |
| 285 290 295                                                     |       |
| cga gcg tac atg aac acc ccg ggg ctt ccc gtg tgc cag gac cat ctt | 13623 |
| Arg Ala Tyr Met Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu |       |
| 300 305 310 315                                                 |       |
| gaa ttt tgg gag ggc gtc ttt aca ggc ctc act cat ata gat gcc cac | 13671 |
| Glu Phe Trp Glu Gly Val Phe Thr Gly Leu Thr His Ile Asp Ala His |       |
| 320 325 330                                                     |       |
| ttt cta tcc cag aca aag cag agt ggg gag aac ctt cct tac ctg gta | 13719 |
| Phe Leu Ser Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val |       |
| 335 340 345                                                     |       |
| gcg tac caa gcc acc gtg tgc gct agg gct caa gcc cct ccc cca tcg | 13767 |
| Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser |       |
| 350 355 360                                                     |       |
| tgg gac cag atg tgg aag tgt ttg att cgc ctc aag ccc acc ctc cat | 13815 |
| Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His |       |
| 365 370 375                                                     |       |
| ggg cca aca ccc ctg cta tac aga ctg ggc gct gtt cag aat gaa atc | 13863 |
| Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile |       |
| 380 385 390 395                                                 |       |
| acc ctg acg cac cca gtc acc aaa tac atc atg aca tgc atg tcg gcc | 13911 |
| Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala |       |
| 400 405 410                                                     |       |
| gac ctg gag gtc gtc acg agc acc tgg gtg ctc gtt ggc ggc gtc ctg | 13959 |
| Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu |       |
| 415 420 425                                                     |       |
| gct gct ttg gcc gcg tat tgc ctg tca aca ggc tgc gtg gtc ata gtg | 14007 |
| Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val |       |
| 430 435 440                                                     |       |
| ggc agg gtc gtc ttg tcc ggg aag ccg gca atc ata cct gac agg gaa | 14055 |
| Gly Arg Val Val Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu |       |
| 445 450 455                                                     |       |



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|-----------------------------------------------------------------|-------|
| gtc ctc tac cga gag ttc gat gag atg gaa gag tgc tct cag cac tta | 14103 |
| Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu |       |
| 460 465 470 475                                                 |       |
| ccg tac atc gag caa ggg atg atg ctc gcc gag cag ttc aag cag aag | 14151 |
| Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys |       |
| 480 485 490                                                     |       |
| gcc ctc ggc ctc ctg cag acc gcg tcc cgt cag gca gag gtt atc gcc | 14199 |
| Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala |       |
| 495 500 505                                                     |       |
| cct gct gtc cag acc aac tgg caa aaa ctc gag acc ttc tgg gcg aag | 14247 |
| Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys |       |
| 510 515 520                                                     |       |
| cat atg tgg aac ttc atc agt ggg ata caa tac ttg gcg ggc ttg tca | 14295 |
| His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser |       |
| 525 530 535                                                     |       |
| acg ctg cct ggt aac ccc gcc att gct tca ttg atg gct ttt aca gct | 14343 |
| Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala |       |
| 540 545 550 555                                                 |       |
| gct gtc acc agc cca cta acc act agc caa acc ctc ctc ttc aac ata | 14391 |
| Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile |       |
| 560 565 570                                                     |       |
| ttg ggg ggg tgg gtg gct gcc cag ctc gcc gcc ccc ggt gcc gct act | 14439 |
| Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr |       |
| 575 580 585                                                     |       |
| gcc ttt gtg ggc gct ggc tta gct ggc gcc gcc atc ggc agt gtt gga | 14487 |
| Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly |       |
| 590 595 600                                                     |       |
| ctg ggg aag gtc ctc ata gac atc ctt gca ggg tat ggc gcg ggc gtg | 14535 |
| Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val |       |
| 605 610 615                                                     |       |
| gcg gga gct ctt gtg gca ttc aag atc atg agc ggt gag gtc ccc tcc | 14583 |
| Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser |       |
| 620 625 630 635                                                 |       |
| acg gag gac ctg gtc aat cta ctg ccc gcc atc ctc tcg ccc gga gcc | 14631 |
| Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala |       |
| 640 645 650                                                     |       |
| ctc gta gtc ggc gtg gtc tgt gca gca ata ctg cgc cgg cac gtt ggc | 14679 |
| Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly |       |
| 655 660 665                                                     |       |
| ccg ggc gag ggg gca gtg cag tgg atg aac cgg ctg ata gcc ttc gcc | 14727 |
| Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala |       |
| 670 675 680                                                     |       |
| tcc cgg ggg aac cat gtt tcc ccc acg cac tac gtg ccg gag agc gat | 14775 |
| Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp |       |
| 685 690 695                                                     |       |

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|-----------------------------------------------------------------|-------|
| gca gct gcc cgc gtc act gcc ata ctc agc agc ctc act gta acc cag | 14823 |
| Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln |       |
| 700 705 710 715                                                 |       |
| ctc ctg agg cga ctg cac cag tgg ata agc tcg gag tgt acc act cca | 14871 |
| Leu Leu Arg Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro |       |
| 720 725 730                                                     |       |
| tgc tcc ggt tcc tgg cta agg gac atc tgg gac tgg ata tgc gag gtg | 14919 |
| Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val |       |
| 735 740 745                                                     |       |
| ttg agc gac ttt aag acc tgg cta aaa gct aag ctc atg cca cag ctg | 14967 |
| Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu |       |
| 750 755 760                                                     |       |
| cct ggg atc ccc ttt gtg tcc tgc cag cgc ggg tat aag ggg gtc tgg | 15015 |
| Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp |       |
| 765 770 775                                                     |       |
| cga ggg gac ggc atc atg cac act cgc tgc cac tgt gga gct gag atc | 15063 |
| Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile |       |
| 780 785 790 795                                                 |       |
| act gga cat gtc aaa aac ggg acg atg agg atc gtc ggt cct agg acc | 15111 |
| Thr Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr |       |
| 800 805 810                                                     |       |
| tgc agg aac atg tgg agt ggg acc ttc ccc att aat gcc tac acc acg | 15159 |
| Cys Arg Asn Met Trp Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr |       |
| 815 820 825                                                     |       |
| ggc ccc tgt acc ccc ctt cct gcg ccg aac tac acg ttc gcg cta tgg | 15207 |
| Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp |       |
| 830 835 840                                                     |       |
| agg gtg tct gca gag gaa tac gtg gag ata agg cag gtg ggg gac ttc | 15255 |
| Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe |       |
| 845 850 855                                                     |       |
| cac tac gtg acg ggt atg act act gac aat ctt aaa tgc ccg tgc cag | 15303 |
| His Tyr Val Thr Gly Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln |       |
| 860 865 870 875                                                 |       |
| gtc cca tcg ccc gaa ttt ttc aca gaa ttg gac ggg gtg cgc cta cat | 15351 |
| Val Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His |       |
| 880 885 890                                                     |       |
| agg ttt gcg ccc ccc tgc aag ccc ttg ctg cgg gag gag gta tca ttc | 15399 |
| Arg Phe Ala Pro Pro Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe |       |
| 895 900 905                                                     |       |
| aga gta gga ctc cac gaa tac ccg gta ggg tcg caa tta cct tgc gag | 15447 |
| Arg Val Gly Leu His Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu |       |
| 910 915 920                                                     |       |
| ccc gaa ccg gac gtg gcc gtg ttg acg tcc atg ctc act gat ccc tcc | 15495 |
| Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser |       |
| 925 930 935                                                     |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| cat ata aca gca gag gcg gcc ggg cga agg ttg gcg agg gga tca ccc | 15543 |
| His Ile Thr Ala Glu Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro     |       |
| 940 945 950 955                                                 |       |
| ccc tct gtg gcc agc tcc tcg gct agc cag cta tcc gct cca tct ctc | 15591 |
| Pro Ser Val Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu |       |
| 960 965 970                                                     |       |
| aag gca act tgc acc gct aac cat gac tcc cct gat gct gag ctc ata | 15639 |
| Lys Ala Thr Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile |       |
| 975 980 985                                                     |       |
| gag gcc aac ctc cta tgg agg cag gag atg ggc ggc aac atc acc agg | 15687 |
| Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg |       |
| 990 995 1000                                                    |       |
| gtt gag tca gaa aac aaa gtg gtg att ctg gac tcc ttc gat ccg ctt | 15735 |
| Val Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu |       |
| 1005 1010 1015                                                  |       |
| gtg gcg gag gag gac gag cgg gag atc tcc gta ccc gca gaa atc ctg | 15783 |
| Val Ala Glu Glu Asp Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu |       |
| 1020 1025 1030 1035                                             |       |
| cgg aag tct cgg aga ttc gcc cag gcc ctg ccc gtt tgg gcg cgg ccg | 15831 |
| Arg Lys Ser Arg Arg Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro |       |
| 1040 1045 1050                                                  |       |
| gac tat aac ccc ccg cta gtg gag acg tgg aaa aag ccc gac tac gaa | 15879 |
| Asp Tyr Asn Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu |       |
| 1055 1060 1065                                                  |       |
| cca cct gtg gtc cat ggc tgc ccg ctt cca cct cca aag tcc cct cct | 15927 |
| Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro |       |
| 1070 1075 1080                                                  |       |
| gtg cct ccg cct cgg aag aag cgg acg gtg gtc ctc act gaa tca acc | 15975 |
| Val Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr |       |
| 1085 1090 1095                                                  |       |
| cta tct act gcc ttg gcc gag ctc gcc acc aga agc ttt ggc agc tcc | 16023 |
| Leu Ser Thr Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser |       |
| 1100 1105 1110 1115                                             |       |
| tca act tcc ggc att acg ggc gac aat acg aca aca tcc tct gag ccc | 16071 |
| Ser Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro |       |
| 1120 1125 1130                                                  |       |
| gcc cct tct ggc tgc ccc ccc gac tcc gac gct gag tcc tat tcc tcc | 16119 |
| Ala Pro Ser Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser |       |
| 1135 1140 1145                                                  |       |
| atg ccc ccc ctg gag ggg gag cct ggg gat ccg gat ctt agc gac ggg | 16167 |
| Met Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly |       |
| 1150 1155 1160                                                  |       |
| tca tgg tca acg gtc agt agt gag gcc aac gcg gag gat gtc gtg tgc | 16215 |
| Ser Trp Ser Thr Val Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys |       |
| 1165 1170 1175                                                  |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| tgc tca atg tct tac tct tgg aca ggc gca ctc gtc acc ccg tgc gcc | 16263 |
| Cys Ser Met Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala |       |
| 1180 1185 1190 1195                                             |       |
| gcg gaa gaa cag aaa ctg ccc atc aat gca cta agc aac tcg ttg cta | 16311 |
| Ala Glu Glu Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu |       |
| 1200 1205 1210                                                  |       |
| cgt cac cac aat ttg gtg tat tcc acc acc tca cgc agt gct tgc caa | 16359 |
| Arg His His Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln |       |
| 1215 1220 1225                                                  |       |
| agg cag aag aaa gtc aca ttt gac aga ctg caa gtt ctg gac agc cat | 16407 |
| Arg Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His |       |
| 1230 1235 1240                                                  |       |
| tac cag gac gta ctc aag gag gtt aaa gca gcg gcg tca aaa gtg aag | 16455 |
| Tyr Gln Asp Val Leu Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys |       |
| 1245 1250 1255                                                  |       |
| gct aac ttg cta tcc gta gag gaa gct tgc agc ctg acg ccc cca cac | 16503 |
| Ala Asn Leu Leu Ser Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His |       |
| 1260 1265 1270 1275                                             |       |
| tca gcc aaa tcc aag ttt ggt tat ggg gca aaa gac gtc cgt tgc cat | 16551 |
| Ser Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His |       |
| 1280 1285 1290                                                  |       |
| gcc aga aag gcc gta acc cac atc aac tcc gtg tgg aaa gac ctt ctg | 16599 |
| Ala Arg Lys Ala Val Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu |       |
| 1295 1300 1305                                                  |       |
| gaa gac aat gta aca cca ata gac act acc atc atg gct aag aac gag | 16647 |
| Glu Asp Asn Val Thr Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu |       |
| 1310 1315 1320                                                  |       |
| gtt ttc tgc gtt cag cct gag aag ggg ggt cgt aag cca gct cgt ctc | 16695 |
| Val Phe Cys Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu |       |
| 1325 1330 1335                                                  |       |
| atc gtg ttc ccc gat ctg ggc gtg cgc gtg tgc gaa aag atg gct ttg | 16743 |
| Ile Val Phe Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu |       |
| 1340 1345 1350 1355                                             |       |
| tac gac gtg gtt aca aag ctc ccc ttg gcc gtg atg gga agc tcc tac | 16791 |
| Tyr Asp Val Val Thr Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr |       |
| 1360 1365 1370                                                  |       |
| gga ttc caa tac tca cca gga cag cgg gtt gaa ttc ctc gtg caa gcg | 16839 |
| Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala |       |
| 1375 1380 1385                                                  |       |
| tgg aag tcc aag aaa acc cca atg ggg ttc tcg tat gat acc cgc tgc | 16887 |
| Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys |       |
| 1390 1395 1400                                                  |       |
| ttt gac tcc aca gtc act gag agc gac atc cgt acg gag gag gca atc | 16935 |
| Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile |       |
| 1405 1410 1415                                                  |       |

|                                                                                    |       |
|------------------------------------------------------------------------------------|-------|
| tac caa tgt tgt gac ctc gac ccc caa gcc cgc gtg gcc atc aag tcc                    | 16983 |
| Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser                    |       |
| 1420                      1425                      1430                      1435 |       |
| ctc acc gag agg ctt tat gtt ggg ggc cct ctt acc aat tca agg ggg                    | 17031 |
| Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly                    |       |
| 1440                      1445                      1450                           |       |
| gag aac tgc ggc tat cgc agg tgc cgc gcg agc ggc gta ctg aca act                    | 17079 |
| Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr                    |       |
| 1455                      1460                      1465                           |       |
| agc tgt ggt aac acc ctc act tgc tac atc aag gcc cgg gca gcc tgt                    | 17127 |
| Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys                    |       |
| 1470                      1475                      1480                           |       |
| cga gcc gca ggg ctc cag gac tgc acc atg ctc gtg tgt ggc gac gac                    | 17175 |
| Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp                    |       |
| 1485                      1490                      1495                           |       |
| tta gtc gtt atc tgt gaa agc gcg ggg gtc cag gag gac gcg gcg agc                    | 17223 |
| Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser                    |       |
| 1500                      1505                      1510                      1515 |       |
| ctg aga gcc ttc acg gag gct atg acc agg tac tcc gcc ccc cct ggg                    | 17271 |
| Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly                    |       |
| 1520                      1525                      1530                           |       |
| gac ccc cca caa cca gaa tac gac ttg gag ctc ata aca tca tgc tcc                    | 17319 |
| Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser                    |       |
| 1535                      1540                      1545                           |       |
| tcc aac gtg tca gtc gcc cac gac ggc gct gga aag agg gtc tac tac                    | 17367 |
| Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr                    |       |
| 1550                      1555                      1560                           |       |
| ctc acc cgt gac cct aca acc ccc ctc gcg aga gct gcg tgg gag aca                    | 17415 |
| Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr                    |       |
| 1565                      1570                      1575                           |       |
| gca aga cac act cca gtc aat tcc tgg cta ggc aac ata atc atg ttt                    | 17463 |
| Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe                    |       |
| 1580                      1585                      1590                      1595 |       |
| gcc ccc aca ctg tgg gcg agg atg ata ctg atg acc cat ttc ttt agc                    | 17511 |
| Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser                    |       |
| 1600                      1605                      1610                           |       |
| gtc ctt ata gcc agg gac cag ctt gaa cag gcc ctc gat tgc gag atc                    | 17559 |
| Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile                    |       |
| 1615                      1620                      1625                           |       |
| tac ggg gcc tgc tac tcc ata gaa cca ctg gat cta cct cca atc att                    | 17607 |
| Tyr Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile                    |       |
| 1630                      1635                      1640                           |       |
| caa aga ctc cat ggc ctc agc gca ttt tca ctc cac agt tac tct cca                    | 17655 |
| Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro                    |       |
| 1645                      1650                      1655                           |       |

ggt gaa atc aat agg gtg gcc gca tgc ctc aga aaa ctt ggg gta ccg 17703  
 Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro  
 1660 1665 1670 1675  
 ccc ttg cga gct tgg aga cac cgg gcc cgg agc gtc cgc gct agg ctt 17751  
 Pro Leu Arg Ala Trp Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu  
 1680 1685 1690  
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 1695 1700 1705  
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 Trp Ala Val Arg Thr Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly  
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 Gln Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp  
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<211> 1771

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence:  
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| Met | Ala | Ala | Tyr | Ala | Ala | Gln | Gly | Tyr | Lys | Val | Leu | Val | Leu | Asn | Pro |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Ser | Val | Ala | Ala | Thr | Leu | Gly | Phe | Gly | Ala | Tyr | Met | Ser | Lys | Ala | His |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Gly | Ile | Asp | Pro | Asn | Ile | Arg | Thr | Gly | Val | Arg | Thr | Ile | Thr | Thr | Gly |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Ser | Pro | Ile | Thr | Tyr | Ser | Thr | Tyr | Gly | Lys | Phe | Leu | Ala | Asp | Gly | Gly |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Cys | Ser | Gly | Gly | Ala | Tyr | Asp | Ile | Ile | Ile | Cys | Asp | Glu | Cys | His | Ser |
| 65  |     |     |     | 70  |     |     |     |     |     | 75  |     |     |     | 80  |     |
| Thr | Asp | Ala | Thr | Ser | Ile | Leu | Gly | Ile | Gly | Thr | Val | Leu | Asp | Gln | Ala |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro  
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 Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser  
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 Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys  
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 Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala  
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 Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val  
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 Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe  
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 Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro Gln Asp  
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 Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe  
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 Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr  
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 Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn  
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 Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly  
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 Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr  
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 Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln Ala Thr  
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 Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp  
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 Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu  
 370 375 380  
 Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile Thr Leu Thr His Pro  
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 Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala Asp Leu Glu Val Val  
 405 410 415



Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala  
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 Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val Gly Arg Val Val Leu  
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 Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu  
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 Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln  
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 Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu  
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 Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala Pro Ala Val Gln Thr  
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 565 570 575  
 Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala  
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 Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val  
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 Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val  
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 660 665 670  
 Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His  
 675 680 685  
 Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val  
 690 695 700  
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 His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp  
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 Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe  
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 Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile  
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 Met His Thr Arg Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys  
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 Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe Arg Val Gly Leu His  
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 Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val  
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 965 970 975  
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 995 1000 1005  
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 Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser Gly Cys  
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 Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu  
 1140 1145 1150  
 Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val  
 1155 1160 1165  
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 Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala Ala Glu Glu Gln Lys  
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                   1460                  1465                  1470  
 Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu  
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Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly Gln Leu Asp Leu Ser  
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<212> DNA

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<223> Description of Artificial Sequence:

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 80 85 90  
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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |       |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|--|
| Val | Leu | Asp | Gln | Ala | Glu | Thr | Ala | Gly | Ala | Arg | Leu | Val | Val | Leu | Ala |       |  |
|     |     |     | 95  |     |     |     |     | 100 |     |     |     |     | 105 |     |     |       |  |
| acc | gcc | acc | cct | ccg | ggc | tcc | gtc | act | gtg | ccc | cat | ccc | aac | atc | gag | 13047 |  |
| Thr | Ala | Thr | Pro | Pro | Gly | Ser | Val | Thr | Val | Pro | His | Pro | Asn | Ile | Glu |       |  |
|     |     | 110 |     |     |     |     | 115 |     |     |     |     | 120 |     |     |     |       |  |
| gag | gtt | gct | ctg | tcc | acc | acc | gga | gag | atc | cct | ttt | tac | ggc | aag | gct | 13095 |  |
| Glu | Val | Ala | Leu | Ser | Thr | Thr | Gly | Glu | Ile | Pro | Phe | Tyr | Gly | Lys | Ala |       |  |
|     | 125 |     |     |     |     | 130 |     |     |     |     | 135 |     |     |     |     |       |  |
| atc | ccc | ctc | gaa | gta | atc | aag | ggg | ggg | aga | cat | ctc | atc | ttc | tgt | cat | 13143 |  |
| Ile | Pro | Leu | Glu | Val | Ile | Lys | Gly | Gly | Arg | His | Leu | Ile | Phe | Cys | His |       |  |
| 140 |     |     |     |     | 145 |     |     |     |     | 150 |     |     |     |     | 155 |       |  |
| tca | aag | aag | aag | tgc | gac | gaa | ctc | gcc | gca | aag | ctg | gtc | gca | ttg | ggc | 13191 |  |
| Ser | Lys | Lys | Lys | Cys | Asp | Glu | Leu | Ala | Ala | Lys | Leu | Val | Ala | Leu | Gly |       |  |
|     |     |     |     | 160 |     |     |     |     | 165 |     |     |     |     | 170 |     |       |  |
| atc | aat | gcc | gtg | gcc | tac | tac | cgc | ggt | ctt | gac | gtg | tcc | gtc | atc | ccg | 13239 |  |
| Ile | Asn | Ala | Val | Ala | Tyr | Tyr | Arg | Gly | Leu | Asp | Val | Ser | Val | Ile | Pro |       |  |
|     |     | 175 |     |     |     |     |     | 180 |     |     |     |     | 185 |     |     |       |  |
| acc | agc | ggc | gat | gtt | gtc | gtc | gtg | gca | acc | gat | gcc | ctc | atg | acc | ggc | 13287 |  |
| Thr | Ser | Gly | Asp | Val | Val | Val | Val | Ala | Thr | Asp | Ala | Leu | Met | Thr | Gly |       |  |
|     |     | 190 |     |     |     |     | 195 |     |     |     |     | 200 |     |     |     |       |  |
| tat | acc | ggc | gac | ttc | gac | tcg | gtg | ata | gac | tgc | aat | acg | tgt | gtc | acc | 13335 |  |
| Tyr | Thr | Gly | Asp | Phe | Asp | Ser | Val | Ile | Asp | Cys | Asn | Thr | Cys | Val | Thr |       |  |
|     | 205 |     |     |     |     | 210 |     |     |     |     | 215 |     |     |     |     |       |  |
| cag | aca | gtc | gat | ttc | agc | ctt | gac | cct | acc | ttc | acc | att | gag | aca | atc | 13383 |  |
| Gln | Thr | Val | Asp | Phe | Ser | Leu | Asp | Pro | Thr | Phe | Thr | Ile | Glu | Thr | Ile |       |  |
| 220 |     |     |     |     | 225 |     |     |     |     | 230 |     |     |     |     | 235 |       |  |
| acg | ctc | ccc | caa | gat | gct | gtc | tcc | cgc | act | caa | cgt | cgg | ggc | agg | act | 13431 |  |
| Thr | Leu | Pro | Gln | Asp | Ala | Val | Ser | Arg | Thr | Gln | Arg | Arg | Gly | Arg | Thr |       |  |
|     |     |     | 240 |     |     |     |     | 245 |     |     |     |     |     | 250 |     |       |  |
| ggc | agg | ggg | aag | cca | ggc | atc | tac | aga | ttt | gtg | gca | ccg | ggg | gag | cgc | 13479 |  |
| Gly | Arg | Gly | Lys | Pro | Gly | Ile | Tyr | Arg | Phe | Val | Ala | Pro | Gly | Glu | Arg |       |  |
|     |     | 255 |     |     |     |     |     | 260 |     |     |     |     | 265 |     |     |       |  |
| ccc | tcc | ggc | atg | ttc | gac | tcg | tcc | gtc | ctc | tgt | gag | tgc | tat | gac | gca | 13527 |  |
| Pro | Ser | Gly | Met | Phe | Asp | Ser | Ser | Val | Leu | Cys | Glu | Cys | Tyr | Asp | Ala |       |  |
|     |     | 270 |     |     |     |     | 275 |     |     |     |     | 280 |     |     |     |       |  |
| ggc | tgt | gct | tgg | tat | gag | ctc | acg | ccc | gcc | gag | act | aca | gtt | agg | cta | 13575 |  |
| Gly | Cys | Ala | Trp | Tyr | Glu | Leu | Thr | Pro | Ala | Glu | Thr | Thr | Val | Arg | Leu |       |  |
|     | 285 |     |     |     |     | 290 |     |     |     |     | 295 |     |     |     |     |       |  |
| cga | gcg | tac | atg | aac | acc | ccg | ggg | ctt | ccc | gtg | tgc | cag | gac | cat | ctt | 13623 |  |
| Arg | Ala | Tyr | Met | Asn | Thr | Pro | Gly | Leu | Pro | Val | Cys | Gln | Asp | His | Leu |       |  |
| 300 |     |     |     |     | 305 |     |     |     |     | 310 |     |     |     |     | 315 |       |  |
| gaa | ttt | tgg | gag | ggc | gtc | ttt | aca | ggc | ctc | act | cat | ata | gat | gcc | cac | 13671 |  |
| Glu | Phe | Trp | Glu | Gly | Val | Phe | Thr | Gly | Leu | Thr | His | Ile | Asp | Ala | His |       |  |
|     |     |     |     | 320 |     |     |     |     | 325 |     |     |     |     | 330 |     |       |  |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| ttt cta tcc cag aca aag cag agt ggg gag aac ctt cct tac ctg gta | 13719 |
| Phe Leu Ser Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val |       |
| 335 340 345                                                     |       |
| gcg tac caa gcc acc gtg tgc gct agg gct caa gcc cct ccc cca tcg | 13767 |
| Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser |       |
| 350 355 360                                                     |       |
| tgg gac cag atg tgg aag tgt ttg att cgc ctc aag ccc acc ctc cat | 13815 |
| Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His |       |
| 365 370 375                                                     |       |
| ggg cca aca ccc ctg cta tac aga ctg ggc gct gtt cag aat gaa atc | 13863 |
| Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile |       |
| 380 385 390 395                                                 |       |
| acc ctg acg cac cca gtc acc aaa tac atc atg aca tgc atg tcg gcc | 13911 |
| Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala |       |
| 400 405 410                                                     |       |
| gac ctg gag gtc gtc acg agc acc tgg gtg ctc gtt ggc ggc gtc ctg | 13959 |
| Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu |       |
| 415 420 425                                                     |       |
| gct gct ttg gcc gcg tat tgc ctg tca aca ggc tgc gtg gtc ata gtg | 14007 |
| Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val |       |
| 430 435 440                                                     |       |
| ggc agg gtc gtc ttg tcc ggg aag ccg gca atc ata cct gac agg gaa | 14055 |
| Gly Arg Val Val Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu |       |
| 445 450 455                                                     |       |
| gtc ctc tac cga gag ttc gat gag atg gaa gag tgc tct cag cac tta | 14103 |
| Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu |       |
| 460 465 470 475                                                 |       |
| ccg tac atc gag caa ggg atg atg ctc gcc gag cag ttc aag cag aag | 14151 |
| Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys |       |
| 480 485 490                                                     |       |
| gcc ctc ggc ctc ctg cag acc gcg tcc cgt cag gca gag gtt atc gcc | 14199 |
| Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala |       |
| 495 500 505                                                     |       |
| cct gct gtc cag acc aac tgg caa aaa ctc gag acc ttc tgg gcg aag | 14247 |
| Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys |       |
| 510 515 520                                                     |       |
| cat atg tgg aac ttc atc agt ggg ata caa tac ttg gcg ggc ttg tca | 14295 |
| His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser |       |
| 525 530 535                                                     |       |
| acg ctg cct ggt aac ccc gcc att gct tca ttg atg gct ttt aca gct | 14343 |
| Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala |       |
| 540 545 550 555                                                 |       |
| gct gtc acc agc cca cta acc act agc caa acc ctc ctc ttc aac ata | 14391 |
| Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile |       |
| 560 565 570                                                     |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| ttg ggg ggg tgg gtg gct gcc cag ctc gcc gcc ccc ggt gcc gct act | 14439 |
| Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr |       |
| 575 580 585                                                     |       |
| gcc ttt gtg ggc gct ggc tta gct ggc gcc gcc atc ggc agt gtt gga | 14487 |
| Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly |       |
| 590 595 600                                                     |       |
| ctg ggg aag gtc ctc ata gac atc ctt gca ggg tat ggc gcg ggc gtg | 14535 |
| Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val |       |
| 605 610 615                                                     |       |
| gcg gga gct ctt gtg gca ttc aag atc atg agc ggt gag gtc ccc tcc | 14583 |
| Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser |       |
| 620 625 630 635                                                 |       |
| acg gag gac ctg gtc aat cta ctg ccc gcc atc ctc tcg ccc gga gcc | 14631 |
| Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala |       |
| 640 645 650                                                     |       |
| ctc gta gtc ggc gtg gtc tgt gca gca ata ctg cgc cgg cac gtt ggc | 14679 |
| Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly |       |
| 655 660 665                                                     |       |
| ccg ggc gag ggg gca gtg cag tgg atg aac cgg ctg ata gcc ttc gcc | 14727 |
| Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala |       |
| 670 675 680                                                     |       |
| tcc cgg ggg aac cat gtt tcc ccc acg cac tac gtg ccg gag agc gat | 14775 |
| Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp |       |
| 685 690 695                                                     |       |
| gca gct gcc cgc gtc act gcc ata ctc agc agc ctc act gta acc cag | 14823 |
| Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln |       |
| 700 705 710 715                                                 |       |
| ctc ctg agg cga ctg cac cag tgg ata agc tcg gag tgt acc act cca | 14871 |
| Leu Leu Arg Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro |       |
| 720 725 730                                                     |       |
| tgc tcc ggt tcc tgg cta agg gac atc tgg gac tgg ata tgc gag gtg | 14919 |
| Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val |       |
| 735 740 745                                                     |       |
| ttg agc gac ttt aag acc tgg cta aaa gct aag ctc atg cca cag ctg | 14967 |
| Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu |       |
| 750 755 760                                                     |       |
| cct ggg atc ccc ttt gtg tcc tgc cag cgc ggg tat aag ggg gtc tgg | 15015 |
| Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp |       |
| 765 770 775                                                     |       |
| cga ggg gac ggc atc atg cac act cgc tgc cac tgt gga gct gag atc | 15063 |
| Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile |       |
| 780 785 790 795                                                 |       |
| act gga cat gtc aaa aac ggg acg atg agg atc gtc ggt cct agg acc | 15111 |
| Thr Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr |       |
| 800 805 810                                                     |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| tgc agg aac atg tgg agt ggg acc ttc ccc att aat gcc tac acc acg | 15159 |
| Cys Arg Asn Met Trp Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr |       |
| 815 820 825                                                     |       |
| ggc ccc tgt acc ccc ctt cct gcg ccg aac tac acg ttc gcg cta tgg | 15207 |
| Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp |       |
| 830 835 840                                                     |       |
| agg gtg tct gca gag gaa tac gtg gag ata agg cag gtg ggg gac ttc | 15255 |
| Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe |       |
| 845 850 855                                                     |       |
| cac tac gtg acg ggt atg act act gac aat ctt aaa tgc ccg tgc cag | 15303 |
| His Tyr Val Thr Gly Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln |       |
| 860 865 870 875                                                 |       |
| gtc cca tcg ccc gaa ttt ttc aca gaa ttg gac ggg gtg cgc cta cat | 15351 |
| Val Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His |       |
| 880 885 890                                                     |       |
| agg ttt gcg ccc ccc tgc aag ccc ttg ctg cgg gag gag gta tca ttc | 15399 |
| Arg Phe Ala Pro Pro Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe |       |
| 895 900 905                                                     |       |
| aga gta gga ctc cac gaa tac ccg gta ggg tcg caa tta cct tgc gag | 15447 |
| Arg Val Gly Leu His Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu |       |
| 910 915 920                                                     |       |
| ccc gaa ccg gac gtg gcc gtg ttg acg tcc atg ctc act gat ccc tcc | 15495 |
| Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser |       |
| 925 930 935                                                     |       |
| cat ata aca gca gag gcg gcc ggg cga agg ttg gcg agg gga tca ccc | 15543 |
| His Ile Thr Ala Glu Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro |       |
| 940 945 950 955                                                 |       |
| ccc tct gtg gcc agc tcc tcg gct agc cag cta tcc gct cca tct ctc | 15591 |
| Pro Ser Val Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu |       |
| 960 965 970                                                     |       |
| aag gca act tgc acc gct aac cat gac tcc cct gat gct gag ctc ata | 15639 |
| Lys Ala Thr Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile |       |
| 975 980 985                                                     |       |
| gag gcc aac ctc cta tgg agg cag gag atg ggc ggc aac atc acc agg | 15687 |
| Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg |       |
| 990 995 1000                                                    |       |
| gtt gag tca gaa aac aaa gtg gtg att ctg gac tcc ttc gat ccg ctt | 15735 |
| Val Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu |       |
| 1005 1010 1015                                                  |       |
| gtg gcg gag gag gac gag ccg gag atc tcc gta ccc gca gaa atc ctg | 15783 |
| Val Ala Glu Glu Asp Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu |       |
| 1020 1025 1030 1035                                             |       |
| cgg aag tct cgg aga ttc gcc cag gcc ctg ccc gtt tgg gcg ccg ccg | 15831 |
| Arg Lys Ser Arg Arg Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro |       |
| 1040 1045 1050                                                  |       |



|                                                                 |       |
|-----------------------------------------------------------------|-------|
| gac tat aac ccc ccg cta gtg gag acg tgg aaa aag ccc gac tac gaa | 15879 |
| Asp Tyr Asn Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu |       |
| 1055 1060 1065                                                  |       |
| cca cct gtg gtc cat ggc tgc ccg ctt cca cct cca aag tcc cct cct | 15927 |
| Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro |       |
| 1070 1075 1080                                                  |       |
| gtg cct ccg cct cgg aag aag ccg acg gtg gtc ctc act gaa tca acc | 15975 |
| Val Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr |       |
| 1085 1090 1095                                                  |       |
| cta tct act gcc ttg gcc gag ctc gcc acc aga agc ttt ggc agc tcc | 16023 |
| Leu Ser Thr Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser |       |
| 1100 1105 1110 1115                                             |       |
| tca act tcc ggc att acg ggc gac aat acg aca aca tcc tct gag ccc | 16071 |
| Ser Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro |       |
| 1120 1125 1130                                                  |       |
| gcc cct tct ggc tgc ccc ccc gac tcc gac gct gag tcc tat tcc tcc | 16119 |
| Ala Pro Ser Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser |       |
| 1135 1140 1145                                                  |       |
| atg ccc ccc ctg gag ggg gag cct ggg gat ccg gat ctt agc gac ggg | 16167 |
| Met Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly |       |
| 1150 1155 1160                                                  |       |
| tca tgg tca acg gtc agt agt gag gcc aac gcg gag gat gtc gtg tgc | 16215 |
| Ser Trp Ser Thr Val Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys |       |
| 1165 1170 1175                                                  |       |
| tgc tca atg tct tac tct tgg aca ggc gca ctc gtc acc ccg tgc gcc | 16263 |
| Cys Ser Met Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala |       |
| 1180 1185 1190 1195                                             |       |
| gcg gaa gaa cag aaa ctg ccc atc aat gca cta agc aac tcg ttg cta | 16311 |
| Ala Glu Glu Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu |       |
| 1200 1205 1210                                                  |       |
| cgt cac cac aat ttg gtg tat tcc acc acc tca cgc agt gct tgc caa | 16359 |
| Arg His His Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln |       |
| 1215 1220 1225                                                  |       |
| agg cag aag aaa gtc aca ttt gac aga ctg caa gtt ctg gac agc cat | 16407 |
| Arg Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His |       |
| 1230 1235 1240                                                  |       |
| tac cag gac gta ctc aag gag gtt aaa gca gcg gcg tca aaa gtg aag | 16455 |
| Tyr Gln Asp Val Leu Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys |       |
| 1245 1250 1255                                                  |       |
| gct aac ttg cta tcc gta gag gaa gct tgc agc ctg acg ccc cca cac | 16503 |
| Ala Asn Leu Leu Ser Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His |       |
| 1260 1265 1270 1275                                             |       |
| tca gcc aaa tcc aag ttt ggt tat ggg gca aaa gac gtc cgt tgc cat | 16551 |
| Ser Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His |       |
| 1280 1285 1290                                                  |       |

gcc aga aag gcc gta acc cac atc aac tcc gtg tgg aaa gac ctt ctg 16599  
 Ala Arg Lys Ala Val Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu  
 1295 1300 1305

gaa gac aat gta aca cca ata gac act acc atc atg gct aag aac gag 16647  
 Glu Asp Asn Val Thr Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu  
 1310 1315 1320

gtt ttc tgc gtt cag cct gag aag ggg ggt cgt aag cca gct cgt ctc 16695  
 Val Phe Cys Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu  
 1325 1330 1335

atc gtg ttc ccc gat ctg ggc gtg cgc gtg tgc gaa aag atg gct ttg 16743  
 Ile Val Phe Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu  
 1340 1345 1350 1355

tac gac gtg gtt aca aag ctc ccc ttg gcc gtg atg gga agc tcc tac 16791  
 Tyr Asp Val Val Thr Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr  
 1360 1365 1370

gga ttc caa tac tca cca gga cag cgg gtt gaa ttc ctc gtg caa gcg 16839  
 Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala  
 1375 1380 1385

tgg aag tcc aag aaa acc cca atg ggg ttc tcg tat gat acc cgc tgc 16887  
 Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys  
 1390 1395 1400

ttt gac tcc aca gtc act gag agc gac atc cgt acg gag gag gca atc 16935  
 Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile  
 1405 1410 1415

tac caa tgt tgt gac ctc gac ccc caa gcc cgc gtg gcc atc aag tcc 16983  
 Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser  
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ctc acc gag agg ctt tat gtt ggg ggc cct ctt acc aat tca agg ggg 17031  
 Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly  
 1440 1445 1450

gag aac tgc ggc tat cgc agg tgc cgc gcg agc ggc gta ctg aca act 17079  
 Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr  
 1455 1460 1465

agc tgt ggt aac acc ctc act tgc tac atc aag gcc cgg gca gcc tgt 17127  
 Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys  
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cga gcc gca ggg ctc cag gac tgc acc atg ctc gtg tgt ggc gac gac 17175  
 Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp  
 1485 1490 1495

tta gtc gtt atc tgt gaa agc gcg ggg gtc cag gag gac gcg gcg agc 17223  
 Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser  
 1500 1505 1510 1515

ctg aga gcc ttc acg gag gct atg acc agg tac tcc gcc ccc cct ggg 17271  
 Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly  
 1520 1525 1530

|                                                                                                                                                           |       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| gac ccc cca caa cca gaa tac gac ttg gag ctc ata aca tca tgc tcc<br>Asp.Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser<br>1535 1540 1545      | 17319 |
| tcc aac gtg tca gtc gcc cac gac ggc gct gga aag agg gtc tac tac<br>Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr<br>1550 1555 1560      | 17367 |
| ctc acc cgt gac cct aca acc ccc ctc gcg aga gct gcg tgg gag aca<br>Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr<br>1565 1570 1575      | 17415 |
| gca aga cac act cca gtc aat tcc tgg cta ggc aac ata atc atg ttt<br>Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe<br>1580 1585 1590 1595 | 17463 |
| gcc ccc aca ctg tgg gcg agg atg ata ctg atg acc cat ttc ttt agc<br>Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser<br>1600 1605 1610      | 17511 |
| gtc ctt ata gcc agg gac cag ctt gaa cag gcc ctc gat tgc gag atc<br>Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile<br>1615 1620 1625      | 17559 |
| tac ggg gcc tgc tac tcc ata gaa cca ctg gat cta cct cca atc att<br>Tyr Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile<br>1630 1635 1640      | 17607 |
| caa aga ctc cat ggc ctc agc gca ttt tca ctc cac agt tac tct cca<br>Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro<br>1645 1650 1655      | 17655 |
| ggg gaa atc aat agg gtg gcc gca tgc ctc aga aaa ctt ggg gta ccg<br>Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro<br>1660 1665 1670 1675 | 17703 |
| ccc ttg cga gct tgg aga cac cgg gcc cgg agc gtc cgc gct agg ctt<br>Pro Leu Arg Ala Trp Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu<br>1680 1685 1690      | 17751 |
| ctg gcc aga gga ggc agg gct gcc ata tgt ggc aag tac ctc ttc aac<br>Leu Ala Arg Gly Gly Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn<br>1695 1700 1705      | 17799 |
| tgg gca gta aga aca aag ctc aaa ctc act cca ata gcg gcc gct ggc<br>Trp Ala Val Arg Thr Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly<br>1710 1715 1720      | 17847 |
| cag ctg gac ttg tcc ggc tgg ttc acg gct ggc tac agc ggg gga gac<br>Gln Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp<br>1725 1730 1735      | 17895 |
| att tat cac agc gtg tct cat gcc cgg ccc cgc tgg atc tgg ttt tgc<br>Ile Tyr His Ser Val Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys<br>1740 1745 1750 1755 | 17943 |
| cta ctc ctg ctt gct gca ggg gta ggc atc tac ctc ctc ccc aac cga<br>Leu Leu Leu Leu Ala Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg<br>1760 1765 1770      | 17991 |

atg agc acg aat cct aaa cct caa aga aag acc aaa cgt aac acc aac 18039  
 Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn  
 1775 1780 1785

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 Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly  
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gga gtt tac ttg ttg ccg cgc agg ggc cct aga ttg ggt gtg cgc gcg 18135  
 Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala  
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acg aga aag act tcc gag cgg tcg caa cct cga ggt aga cgt cag cct 18183  
 Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro  
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atc ccc aag gct cgt cgg ccc gag ggc agg acc tgg gct cag ccc ggg 18231  
 Ile Pro Lys Ala Arg Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly  
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tac cct tgg ccc ctc tat ggc aat gag ggc tgc ggg tgg gcg gga tgg 18279  
 Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp  
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ctc ctg tct ccc cgt ggc tct cgg cct agc tgg ggc ccc aca gac ccc 18327  
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 Arg Arg Arg Ser Arg Asn Leu Gly Lys  
 1885 1890

actgtacttt tagctcgtac aaaatacaat atactttttca tttctccgta aacaacatgt 18434  
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<210> 13

<211> 1892

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:

pd.delta.NS3NS5.pj.core121

<400> 13

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Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His  
 20 25 30

Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly  
 35 40 45

Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly  
 50 55 60

Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser  
 65 70 75 80

Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala

| 85                                                              |     |                                 |     |     |  |  |  |  |  | 90 |  |  |  |  | 95 |  |  |  |  |
|-----------------------------------------------------------------|-----|---------------------------------|-----|-----|--|--|--|--|--|----|--|--|--|--|----|--|--|--|--|
| Glu Thr Ala Gly Ala Arg Leu Val                                 | 100 | Val Leu Ala Thr Ala Thr Pro Pro | 105 | 110 |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser | 115 | 120                             | 125 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val | 130 | 135                             | 140 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys | 145 | 150                             | 155 | 160 |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala | 165 | 170                             | 175 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val | 180 | 185                             | 190 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe | 195 | 200                             | 205 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe | 210 | 215                             | 220 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro Gln Asp | 225 | 230                             | 235 | 240 |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro | 245 | 250                             | 255 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe | 260 | 265                             | 270 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr | 275 | 280                             | 285 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn | 290 | 295                             | 300 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly | 305 | 310                             | 315 | 320 |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr | 325 | 330                             | 335 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln Ala Thr | 340 | 345                             | 350 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp | 355 | 360                             | 365 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu | 370 | 375                             | 380 |     |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |
| Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile Thr Leu Thr His Pro | 385 | 390                             | 395 | 400 |  |  |  |  |  |    |  |  |  |  |    |  |  |  |  |

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|             |          |         |         |         |         |         |     |     |     |     |     |     |       |
|-------------|----------|---------|---------|---------|---------|---------|-----|-----|-----|-----|-----|-----|-------|
| acaagcttac  | aaaacaaa | atg     | gct     | gca     | tat     | gca     | gct | cag | ggc | tat | aag | gtg | 12711 |
|             |          | Met     | Ala     | Ala     | Tyr     | Ala     | Ala | Gln | Gly | Tyr | Lys | Val |       |
|             |          | 1       |         |         |         | 5       |     |     |     |     | 10  |     |       |
| cta gta ctc | aac ccc  | tct gtt | gct gca | aca ctg | ggc ttt | ggg gct | tac |     |     |     |     |     | 12759 |
| Leu Val Leu | Asn Pro  | Ser Val | Ala Ala | Thr Leu | Gly Phe | Gly Ala | Tyr |     |     |     |     |     |       |
|             | 15       |         | 20      |         | 25      |         |     |     |     |     |     |     |       |
| atg tcc aag | gct cat  | ggg atc | gat cct | aac atc | agg acc | ggg gtg | aga |     |     |     |     |     | 12807 |
| Met Ser Lys | Ala His  | Gly Ile | Asp Pro | Asn Ile | Arg Thr | Gly Val | Arg |     |     |     |     |     |       |
|             | 30       |         | 35      |         | 40      |         |     |     |     |     |     |     |       |
| aca att acc | act ggc  | agc ccc | atc acg | tac tcc | acc tac | ggc aag | ttc |     |     |     |     |     | 12855 |
| Thr Ile Thr | Thr Gly  | Ser Pro | Ile Thr | Tyr Ser | Thr Tyr | Gly Lys | Phe |     |     |     |     |     |       |
|             | 45       |         | 50      |         | 55      |         |     |     |     |     |     |     |       |
| ctt gcc gac | ggc ggg  | tgc tcg | ggg ggc | gct tat | gac ata | ata att | tgt |     |     |     |     |     | 12903 |
| Leu Ala Asp | Gly Gly  | Cys Ser | Gly Gly | Ala Tyr | Asp Ile | Ile Ile | Cys |     |     |     |     |     |       |
| 60          |          | 65      |         | 70      |         | 75      |     |     |     |     |     |     |       |
| gac gag tgc | cac tcc  | acg gat | gcc aca | tcc atc | ttg ggc | att ggc | act |     |     |     |     |     | 12951 |
| Asp Glu Cys | His Ser  | Thr Asp | Ala Thr | Ser Ile | Leu Gly | Ile Gly | Thr |     |     |     |     |     |       |
|             | 80       |         | 85      |         | 90      |         |     |     |     |     |     |     |       |
| gtc ctt gac | caa gca  | gag act | gcg ggg | gcg aga | ctg gtt | gtg ctc | gcc |     |     |     |     |     | 12999 |
| Val Leu Asp | Gln Ala  | Glu Thr | Ala Gly | Ala Arg | Leu Val | Val Leu | Ala |     |     |     |     |     |       |
|             | 95       |         | 100     |         | 105     |         |     |     |     |     |     |     |       |
| acc gcc acc | cct ccg  | ggc tcc | gtc act | gtg ccc | cat ccc | aac atc | gag |     |     |     |     |     | 13047 |
| Thr Ala Thr | Pro Pro  | Gly Ser | Val Thr | Val Pro | His Pro | Asn Ile | Glu |     |     |     |     |     |       |
|             | 110      |         | 115     |         | 120     |         |     |     |     |     |     |     |       |
| gag gtt gct | ctg tcc  | acc acc | gga gag | atc cct | ttt tac | ggc aag | gct |     |     |     |     |     | 13095 |
| Glu Val Ala | Leu Ser  | Thr Thr | Gly Glu | Ile Pro | Phe Tyr | Gly Lys | Ala |     |     |     |     |     |       |
| 125         |          | 130     |         | 135     |         |         |     |     |     |     |     |     |       |
| atc ccc ctc | gaa gta  | atc aag | ggg ggg | aga cat | ctc atc | ttc tgt | cat |     |     |     |     |     | 13143 |
| Ile Pro Leu | Glu Val  | Ile Lys | Gly Gly | Arg His | Leu Ile | Phe Cys | His |     |     |     |     |     |       |
| 140         |          | 145     |         | 150     |         | 155     |     |     |     |     |     |     |       |
| tca aag aag | aag tgc  | gac gaa | ctc gcc | gca aag | ctg gtc | gca ttg | ggc |     |     |     |     |     | 13191 |
| Ser Lys Lys | Lys Cys  | Asp Glu | Leu Ala | Lys Leu | Val Val | Ala Leu | Gly |     |     |     |     |     |       |
|             | 160      |         | 165     |         | 170     |         |     |     |     |     |     |     |       |
| atc aat gcc | gtg gcc  | tac tac | cgc ggt | ctt gac | gtg tcc | gtc atc | ccg |     |     |     |     |     | 13239 |
| Ile Asn Ala | Val Ala  | Tyr Tyr | Arg Gly | Leu Asp | Val Ser | Val Ile | Pro |     |     |     |     |     |       |
|             | 175      |         | 180     |         | 185     |         |     |     |     |     |     |     |       |
| acc agc ggc | gat gtt  | gtc gtc | gtg gca | acc gat | gcc ctc | atg acc | ggc |     |     |     |     |     | 13287 |
| Thr Ser Gly | Asp Val  | Val Val | Val Val | Ala Thr | Asp Ala | Leu Met | Thr |     |     |     |     |     |       |
|             | 190      |         | 195     |         | 200     |         |     |     |     |     |     |     |       |
| tat acc ggc | gac ttc  | gac tcg | gtg ata | gac tgc | aat acg | tgt gtc | acc |     |     |     |     |     | 13335 |
| Tyr Thr Gly | Asp Phe  | Asp Ser | Val Ile | Asp Cys | Asn Thr | Cys Val | Thr |     |     |     |     |     |       |
|             | 205      |         | 210     |         | 215     |         |     |     |     |     |     |     |       |
| cag aca gtc | gat ttc  | agc ctt | gac cct | acc ttc | acc att | gag aca | atc |     |     |     |     |     | 13383 |
| Gln Thr Val | Asp Phe  | Ser Leu | Asp Pro | Thr Phe | Thr Ile | Glu Thr | Ile |     |     |     |     |     |       |
| 220         |          | 225     |         | 230     |         | 235     |     |     |     |     |     |     |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| acg ctc ccc caa gat gct gtc tcc cgc act caa cgt cgg ggc agg act | 13431 |
| Thr Leu Pro Gln Asp Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr |       |
| 240 245 250                                                     |       |
| ggc agg ggg aag cca ggc atc tac aga ttt gtg gca ccg ggg gag cgc | 13479 |
| Gly Arg Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg |       |
| 255 260 265                                                     |       |
| ccc tcc ggc atg ttc gac tcg tcc gtc ctc tgt gag tgc tat gac gca | 13527 |
| Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala |       |
| 270 275 280                                                     |       |
| ggc tgt gct tgg tat gag ctc acg ccc gcc gag act aca gtt agg cta | 13575 |
| Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu |       |
| 285 290 295                                                     |       |
| cga gcg tac atg aac acc ccg ggg ctt ccc gtg tgc cag gac cat ctt | 13623 |
| Arg Ala Tyr Met Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu |       |
| 300 305 310 315                                                 |       |
| gaa ttt tgg gag ggc gtc ttt aca ggc ctc act cat ata gat gcc cac | 13671 |
| Glu Phe Trp Glu Gly Val Phe Thr Gly Leu Thr His Ile Asp Ala His |       |
| 320 325 330                                                     |       |
| ttt cta tcc cag aca aag cag agt ggg gag aac ctt cct tac ctg gta | 13719 |
| Phe Leu Ser Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val |       |
| 335 340 345                                                     |       |
| gcg tac caa gcc acc gtg tgc gct agg gct caa gcc cct ccc cca tcg | 13767 |
| Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser |       |
| 350 355 360                                                     |       |
| tgg gac cag atg tgg aag tgt ttg att cgc ctc aag ccc acc ctc cat | 13815 |
| Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His |       |
| 365 370 375                                                     |       |
| ggg cca aca ccc ctg cta tac aga ctg ggc gct gtt cag aat gaa atc | 13863 |
| Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile |       |
| 380 385 390 395                                                 |       |
| acc ctg acg cac cca gtc acc aaa tac atc atg aca tgc atg tcg gcc | 13911 |
| Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala |       |
| 400 405 410                                                     |       |
| gac ctg gag gtc gtc acg agc acc tgg gtg ctc gtt ggc ggc gtc ctg | 13959 |
| Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu |       |
| 415 420 425                                                     |       |
| gct gct ttg gcc gcg tat tgc ctg tca aca ggc tgc gtg gtc ata gtg | 14007 |
| Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val |       |
| 430 435 440                                                     |       |
| ggc agg gtc gtc ttg tcc ggg aag ccg gca atc ata cct gac agg gaa | 14055 |
| Gly Arg Val Val Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu |       |
| 445 450 455                                                     |       |
| gtc ctc tac cga gag ttc gat gag atg gaa gag tgc tct cag cac tta | 14103 |
| Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Cys Ser Gln His Leu     |       |
| 460 465 470 475                                                 |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| ccg tac atc gag caa ggg atg atg ctc gcc gag cag ttc aag cag aag | 14151 |
| Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys |       |
| 480 485 490                                                     |       |
| gcc ctc ggc ctc ctg cag acc gcg tcc cgt cag gca gag gtt atc gcc | 14199 |
| Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala |       |
| 495 500 505                                                     |       |
| cct gct gtc cag acc aac tgg caa aaa ctc gag acc ttc tgg gcg aag | 14247 |
| Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys |       |
| 510 515 520                                                     |       |
| cat atg tgg aac ttc atc agt ggg ata caa tac ttg gcg ggc ttg tca | 14295 |
| His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser |       |
| 525 530 535                                                     |       |
| acg ctg cct ggt aac ccc gcc att gct tca ttg atg gct ttt aca gct | 14343 |
| Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala |       |
| 540 545 550 555                                                 |       |
| gct gtc acc agc cca cta acc act agc caa acc ctc ctc ttc aac ata | 14391 |
| Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile |       |
| 560 565 570                                                     |       |
| ttg ggg ggg tgg gtg gct gcc cag ctc gcc gcc ccc ggt gcc gct act | 14439 |
| Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr |       |
| 575 580 585                                                     |       |
| gcc ttt gtg ggc gct ggc tta gct ggc gcc gcc atc ggc agt gtt gga | 14487 |
| Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly |       |
| 590 595 600                                                     |       |
| ctg ggg aag gtc ctc ata gac atc ctt gca ggg tat ggc gcg ggc gtg | 14535 |
| Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val |       |
| 605 610 615                                                     |       |
| gcg gga gct ctt gtg gca ttc aag atc atg agc ggt gag gtc ccc tcc | 14583 |
| Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser |       |
| 620 625 630 635                                                 |       |
| acg gag gac ctg gtc aat cta ctg ccc gcc atc ctc tcg ccc gga gcc | 14631 |
| Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala |       |
| 640 645 650                                                     |       |
| ctc gta gtc ggc gtg gtc tgt gca gca ata ctg cgc cgg cac gtt ggc | 14679 |
| Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly |       |
| 655 660 665                                                     |       |
| ccg ggc gag ggg gca gtg cag tgg atg aac cgg ctg ata gcc ttc gcc | 14727 |
| Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala |       |
| 670 675 680                                                     |       |
| tcc cgg ggg aac cat gtt tcc ccc acg cac tac gtg ccg gag agc gat | 14775 |
| Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp |       |
| 685 690 695                                                     |       |
| gca gct gcc cgc gtc act gcc ata ctc agc agc ctc act gta acc cag | 14823 |
| Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln |       |
| 700 705 710 715                                                 |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| ctc ctg agg cga ctg cac cag tgg ata agc tcg gag tgt acc act cca | 14871 |
| Leu Leu Arg Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro |       |
| 720 725 730                                                     |       |
| tgc tcc ggt tcc tgg cta agg gac atc tgg gac tgg ata tgc gag gtg | 14919 |
| Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val |       |
| 735 740 745                                                     |       |
| ttg agc gac ttt aag acc tgg cta aaa gct aag ctc atg cca cag ctg | 14967 |
| Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu |       |
| 750 755 760                                                     |       |
| cct ggg atc ccc ttt gtg tcc tgc cag cgc ggg tat aag ggg gtc tgg | 15015 |
| Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp |       |
| 765 770 775                                                     |       |
| cga ggg gac ggc atc atg cac act cgc tgc cac tgt gga gct gag atc | 15063 |
| Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile |       |
| 780 785 790 795                                                 |       |
| act gga cat gtc aaa aac ggg acg atg agg atc gtc ggt cct agg acc | 15111 |
| Thr Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr |       |
| 800 805 810                                                     |       |
| tgc agg aac atg tgg agt ggg acc ttc ccc att aat gcc tac acc acg | 15159 |
| Cys Arg Asn Met Trp Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr |       |
| 815 820 825                                                     |       |
| ggc ccc tgt acc ccc ctt cct gcg ccg aac tac acg ttc gcg cta tgg | 15207 |
| Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp |       |
| 830 835 840                                                     |       |
| agg gtg tct gca gag gaa tac gtg gag ata agg cag gtg ggg gac ttc | 15255 |
| Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe |       |
| 845 850 855                                                     |       |
| cac tac gtg acg ggt atg act act gac aat ctt aaa tgc ccg tgc cag | 15303 |
| His Tyr Val Thr Gly Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln |       |
| 860 865 870 875                                                 |       |
| gtc cca tcg ccc gaa ttt ttc aca gaa ttg gac ggg gtg cgc cta cat | 15351 |
| Val Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His |       |
| 880 885 890                                                     |       |
| agg ttt gcg ccc ccc tgc aag ccc ttg ctg cgg gag gag gta tca ttc | 15399 |
| Arg Phe Ala Pro Pro Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe |       |
| 895 900 905                                                     |       |
| aga gta gga ctc cac gaa tac ccg gta ggg tcg caa tta cct tgc gag | 15447 |
| Arg Val Gly Leu His Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu |       |
| 910 915 920                                                     |       |
| ccc gaa ccg gac gtg gcc gtg ttg acg tcc atg ctc act gat ccc tcc | 15495 |
| Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser |       |
| 925 930 935                                                     |       |
| cat ata aca gca gag gcg gcc ggg cga agg ttg gcg agg gga tca ccc | 15543 |
| His Ile Thr Ala Glu Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro |       |
| 940 945 950 955                                                 |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| ccc tct gtg gcc agc tcc tcg gct agc cag cta tcc gct cca tct ctc | 15591 |
| Pro Ser Val Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu |       |
| 960 965 970                                                     |       |
| aag gca act tgc acc gct aac cat gac tcc cct gat gct gag ctc ata | 15639 |
| Lys Ala Thr Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile |       |
| 975 980 985                                                     |       |
| gag gcc aac ctc cta tgg agg cag gag atg ggc ggc aac atc acc agg | 15687 |
| Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg |       |
| 990 995 1000                                                    |       |
| gtt gag tca gaa aac aaa gtg gtg att ctg gac tcc ttc gat ccg ctt | 15735 |
| Val Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu |       |
| 1005 1010 1015                                                  |       |
| gtg gcg gag gag gac gag cgg gag atc tcc gta ccc gca gaa atc ctg | 15783 |
| Val Ala Glu Glu Asp Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu |       |
| 1020 1025 1030 1035                                             |       |
| cgg aag tct cgg aga ttc gcc cag gcc ctg ccc gtt tgg gcg cgg ccg | 15831 |
| Arg Lys Ser Arg Arg Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro |       |
| 1040 1045 1050                                                  |       |
| gac tat aac ccc ccg cta gtg gag acg tgg aaa aag ccc gac tac gaa | 15879 |
| Asp Tyr Asn Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu |       |
| 1055 1060 1065                                                  |       |
| cca cct gtg gtc cat ggc tgc ccg ctt cca cct cca aag tcc cct cct | 15927 |
| Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro |       |
| 1070 1075 1080                                                  |       |
| gtg cct ccg cct cgg aag aag cgg acg gtg gtc ctc act gaa tca acc | 15975 |
| Val Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr |       |
| 1085 1090 1095                                                  |       |
| cta tct act gcc ttg gcc gag ctc gcc acc aga agc ttt ggc agc tcc | 16023 |
| Leu Ser Thr Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser |       |
| 1100 1105 1110 1115                                             |       |
| tca act tcc ggc att acg ggc gac aat acg aca aca tcc tct gag ccc | 16071 |
| Ser Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro |       |
| 1120 1125 1130                                                  |       |
| gcc cct tct ggc tgc ccc ccc gac tcc gac gct gag tcc tat tcc tcc | 16119 |
| Ala Pro Ser Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser |       |
| 1135 1140 1145                                                  |       |
| atg ccc ccc ctg gag ggg gag cct ggg gat ccg gat ctt agc gac ggg | 16167 |
| Met Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly |       |
| 1150 1155 1160                                                  |       |
| tca tgg tca acg gtc agt agt gag gcc aac gcg gag gat gtc gtg tgc | 16215 |
| Ser Trp Ser Thr Val Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys |       |
| 1165 1170 1175                                                  |       |
| tgc tca atg tct tac tct tgg aca ggc gca ctc gtc acc ccg tgc gcc | 16263 |
| Cys Ser Met Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala |       |
| 1180 1185 1190 1195                                             |       |

|                                                                  |       |
|------------------------------------------------------------------|-------|
| gcg gaa gaa cag aaa ctg ccc atc aat gca cta agc aac tcg ttg cta  | 16311 |
| Ala Glu Glu Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu  |       |
| 1200 1205 1210                                                   |       |
| cggt cac cac aat ttg gtg tat tcc acc acc tca cgc agt gct tgc caa | 16359 |
| Arg His His Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln  |       |
| 1215 1220 1225                                                   |       |
| agg cag aag aaa gtc aca ttt gac aga ctg caa gtt ctg gac agc cat  | 16407 |
| Arg Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His  |       |
| 1230 1235 1240                                                   |       |
| tac cag gac gta ctc aag gag gtt aaa gca gcg gcg tca aaa gtg aag  | 16455 |
| Tyr Gln Asp Val Leu Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys  |       |
| 1245 1250 1255                                                   |       |
| gct aac ttg cta tcc gta gag gaa gct tgc agc ctg acg ccc cca cac  | 16503 |
| Ala Asn Leu Leu Ser Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His  |       |
| 1260 1265 1270 1275                                              |       |
| tca gcc aaa tcc aag ttt ggt tat ggg gca aaa gac gtc cgt tgc cat  | 16551 |
| Ser Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His  |       |
| 1280 1285 1290                                                   |       |
| gcc aga aag gcc gta acc cac atc aac tcc gtg tgg aaa gac ctt ctg  | 16599 |
| Ala Arg Lys Ala Val Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu  |       |
| 1295 1300 1305                                                   |       |
| gaa gac aat gta aca cca ata gac act acc atc atg gct aag aac gag  | 16647 |
| Glu Asp Asn Val Thr Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu  |       |
| 1310 1315 1320                                                   |       |
| gtt ttc tgc gtt cag cct gag aag ggg ggt cgt aag cca gct cgt ctc  | 16695 |
| Val Phe Cys Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu  |       |
| 1325 1330 1335                                                   |       |
| atc gtg ttc ccc gat ctg ggc gtg cgc gtg tgc gaa aag atg gct ttg  | 16743 |
| Ile Val Phe Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu  |       |
| 1340 1345 1350 1355                                              |       |
| tac gac gtg gtt aca aag ctc ccc ttg gcc gtg atg gga agc tcc tac  | 16791 |
| Tyr Asp Val Val Thr Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr  |       |
| 1360 1365 1370                                                   |       |
| gga ttc caa tac tca cca gga cag cgg gtt gaa ttc ctc gtg caa gcg  | 16839 |
| Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala  |       |
| 1375 1380 1385                                                   |       |
| tgg aag tcc aag aaa acc cca atg ggg ttc tcg tat gat acc cgc tgc  | 16887 |
| Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys  |       |
| 1390 1395 1400                                                   |       |
| ttt gac tcc aca gtc act gag agc gac atc cgt acg gag gag gca atc  | 16935 |
| Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile  |       |
| 1405 1410 1415                                                   |       |
| tac caa tgt tgt gac ctc gac ccc caa gcc cgc gtg gcc atc aag tcc  | 16983 |
| Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser  |       |
| 1420 1425 1430 1435                                              |       |



ctc acc gag agg ctt tat gtt ggg ggc cct ctt acc aat tca agg ggg 17031  
 Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly  
                   1440                  1445                  1450

gag aac tgc ggc tat cgc agg tgc cgc gcg agc ggc gta ctg aca act 17079  
 Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr  
                   1455                  1460                  1465

agc tgt ggt aac acc ctc act tgc tac atc aag gcc cgg gca gcc tgt 17127  
 Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys  
                   1470                  1475                  1480

cga gcc gca ggg ctc cag gac tgc acc atg ctc gtg tgt ggc gac gac 17175  
 Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp  
                   1485                  1490                  1495

tta gtc gtt atc tgt gaa agc gcg ggg gtc cag gag gac gcg gcg agc 17223  
 Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser  
 1500                  1505                  1510                  1515

ctg aga gcc ttc acg gag gct atg acc agg tac tcc gcc ccc cct ggg 17271  
 Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly  
                   1520                  1525                  1530

gac ccc cca caa cca gaa tac gac ttg gag ctc ata aca tca tgc tcc 17319  
 Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser  
                   1535                  1540                  1545

tcc aac gtg tca gtc gcc cac gac ggc gct gga aag agg gtc tac tac 17367  
 Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr  
                   1550                  1555                  1560

ctc acc cgt gac cct aca acc ccc ctc gcg aga gct gcg tgg gag aca 17415  
 Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr  
                   1565                  1570                  1575

gca aga cac act cca gtc aat tcc tgg cta ggc aac ata atc atg ttt 17463  
 Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe  
 1580                  1585                  1590                  1595

gcc ccc aca ctg tgg gcg agg atg ata ctg atg acc cat ttc ttt agc 17511  
 Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser  
                   1600                  1605                  1610

gtc ctt ata gcc agg gac cag ctt gaa cag gcc ctc gat tgc gag atc 17559  
 Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile  
                   1615                  1620                  1625

tac ggg gcc tgc tac tcc ata gaa cca ctg gat cta cct cca atc att 17607  
 Tyr Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile  
                   1630                  1635                  1640

caa aga ctc cat ggc ctc agc gca ttt tca ctc cac agt tac tct cca 17655  
 Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro  
                   1645                  1650                  1655

ggt gaa atc aat agg gtg gcc gca tgc ctc aga aaa ctt ggg gta ccg 17703  
 Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro  
 1660                  1665                  1670                  1675

ccc ttg cga gct tgg aga cac cgg gcc cgg agc gtc cgc gct agg ctt 17751  
 Pro Leu Arg Ala Trp Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu  
 1680 1685 1690

ctg gcc aga gga ggc agg gct gcc ata tgt ggc aag tac ctc ttc aac 17799  
 Leu Ala Arg Gly Gly Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn  
 1695 1700 1705

tgg gca gta aga aca aag ctc aaa ctc act cca ata gcg gcc gct ggc 17847  
 Trp Ala Val Arg Thr Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly  
 1710 1715 1720

cag ctg gac ttg tcc ggc tgg ttc acg gct ggc tac agc ggg gga gac 17895  
 Gln Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp  
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att tat cac agc gtg tct cat gcc cgg ccc cgc tgg atc tgg ttt tgc 17943  
 Ile Tyr His Ser Val Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys  
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cta ctc ctg ctt gct gca ggg gta ggc atc tac ctc ctc ccc aac cga 17991  
 Leu Leu Leu Leu Ala Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg  
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atg agc acg aat cct aaa cct caa aga aag acc aaa cgt aac acc aac 18039  
 Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn  
 1775 1780 1785

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 Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly  
 1790 1795 1800

gga gtt tac ttg ttg ccg cgc agg ggc cct aga ttg ggt gtg cgc gcg 18135  
 Gly Val Tyr Leu Leu Pro Arg Gly Pro Arg Leu Gly Val Arg Ala  
 1805 1810 1815

acg aga aag act tcc gag cgg tcg caa cct cga ggt aga cgt cag cct 18183  
 Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro  
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atc ccc aag gct cgt cgg ccc gag ggc agg acc tgg gct cag ccc ggg 18231  
 Ile Pro Lys Ala Arg Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly  
 1840 1845 1850

tac cct tgg ccc ctc tat ggc aat gag ggc tgc ggg tgg gcg gga tgg 18279  
 Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp  
 1855 1860 1865

ctc ctg tct ccc cgt ggc tct cgg cct agc tgg ggc ccc aca gac ccc 18327  
 Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro  
 1870 1875 1880

cgg cgt agg tcg cgc aat ttg ggt aag gtc atc gat acc ctt acg tgc 18375  
 Arg Arg Arg Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys  
 1885 1890 1895

ggc ttc gcc gac ctc atg ggg tac ata ccg ctc gtc ggc gcc cct ctt 18423  
 Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu  
 1900 1905 1910 1915

gga ggc gct gcc agg gcc ctg gcg cat ggc gtc cgg gtt ctg gaa gac 18471  
 Gly Gly Ala Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp  
                   1920                                  1925                                  1930

ggc gtg aac tat gca aca ggg aac ctt cct ggt tgc tct taatagtcga 18520  
 Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser  
                   1935                                  1940

ctttgttccc actgtacttt tagctcgtac aaaatacaat atacttttca tttctccgta 18580  
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<210> 15

<211> 1944

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:

pd.delta.NS3NS5.pj.core173

<400> 15

Met Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro  
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 20 25 30

Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly  
 35 40 45

Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly  
 50 55 60

Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser  
 65 70 75 80

Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala  
 85 90 95

Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro  
 100 105 110

Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser  
 115 120 125

Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val  
 130 135 140

Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys  
 145 150 155 160

Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala  
 165 170 175

Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val  
 180 185 190

Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe  
 195 200 205

Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe

| 210                                                                                | 215 | 220 |
|------------------------------------------------------------------------------------|-----|-----|
| Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro Gln Asp<br>225 230 235 240 |     |     |
| Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro<br>245 250 255     |     |     |
| Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe<br>260 265 270     |     |     |
| Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr<br>275 280 285     |     |     |
| Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn<br>290 295 300     |     |     |
| Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly<br>305 310 315 320 |     |     |
| Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr<br>325 330 335     |     |     |
| Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln Ala Thr<br>340 345 350     |     |     |
| Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp<br>355 360 365     |     |     |
| Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu<br>370 375 380     |     |     |
| Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile Thr Leu Thr His Pro<br>385 390 395 400 |     |     |
| Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala Asp Leu Glu Val Val<br>405 410 415     |     |     |
| Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala<br>420 425 430     |     |     |
| Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val Gly Arg Val Val Leu<br>435 440 445     |     |     |
| Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu<br>450 455 460     |     |     |
| Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln<br>465 470 475 480 |     |     |
| Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu<br>485 490 495     |     |     |
| Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala Pro Ala Val Gln Thr<br>500 505 510     |     |     |
| Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys His Met Trp Asn Phe<br>515 520 525     |     |     |

Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn  
 530 535 540  
 Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro  
 545 550 555 560  
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Met Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val
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Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr
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atg tcc aag gct cat ggg atc gat cct aac atc agg acc ggg gtg aga 12807
Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg
30 35 40
aca att acc act ggc agc ccc atc acg tac tcc acc tac ggc aag ttc 12855
Thr Ile Thr Thr Gly Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe
45 50 55

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|-----------------------------------------------------------------|-------|
| ctt gcc gac ggc ggg tgc tcg ggg ggc gct tat gac ata ata att tgt | 12903 |
| Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Il Ile Cys  |       |
| 60 65 70 75                                                     |       |
| gac gag tgc cac tcc acg gat gcc aca tcc atc ttg ggc att ggc act | 12951 |
| Asp Glu Cys His Ser Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr |       |
| 80 85 90                                                        |       |
| gtc ctt gac caa gca gag act gcg ggg gcg aga ctg gtt gtg ctc gcc | 12999 |
| Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala |       |
| 95 100 105                                                      |       |
| acc gcc acc cct ccg ggc tcc gtc act gtg ccc cat ccc aac atc gag | 13047 |
| Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu |       |
| 110 115 120                                                     |       |
| gag gtt gct ctg tcc acc acc gga gag atc cct ttt tac ggc aag gct | 13095 |
| Glu Val Ala Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala |       |
| 125 130 135                                                     |       |
| atc ccc ctc gaa gta atc aag ggg ggg aga cat ctc atc ttc tgt cat | 13143 |
| Ile Pro Leu Glu Val Ile Lys Gly Gly Arg His Leu Ile Phe Cys His |       |
| 140 145 150 155                                                 |       |
| tca aag aag aag tgc gac gaa ctc gcc gca aag ctg gtc gca ttg ggc | 13191 |
| Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly |       |
| 160 165 170                                                     |       |
| atc aat gcc gtg gcc tac tac cgc ggt ctt gac gtg tcc gtc atc ccg | 13239 |
| Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro |       |
| 175 180 185                                                     |       |
| acc agc ggc gat gtt gtc gtc gtg gca acc gat gcc ctc atg acc ggc | 13287 |
| Thr Ser Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly |       |
| 190 195 200                                                     |       |
| tat acc ggc gac ttc gac tcg gtg ata gac tgc aat acg tgt gtc acc | 13335 |
| Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr |       |
| 205 210 215                                                     |       |
| cag aca gtc gat ttc agc ctt gac cct acc ttc acc att gag aca atc | 13383 |
| Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile |       |
| 220 225 230 235                                                 |       |
| acg ctc ccc caa gat gct gtc tcc cgc act caa cgt cgg ggc agg act | 13431 |
| Thr Leu Pro Gln Asp Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr |       |
| 240 245 250                                                     |       |
| ggc agg ggg aag cca ggc atc tac aga ttt gtg gca ccg ggg gag cgc | 13479 |
| Gly Arg Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg |       |
| 255 260 265                                                     |       |
| ccc tcc ggc atg ttc gac tcg tcc gtc ctc tgt gag tgc tat gac gca | 13527 |
| Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala |       |
| 270 275 280                                                     |       |
| ggc tgt gct tgg tat gag ctc acg ccc gcc gag act aca gtt agg cta | 13575 |
| Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu |       |
| 285 290 295                                                     |       |

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|-----------------------------------------------------------------|-------|
| cga gcg tac atg aac acc ccg ggg ctt ccc gtg tgc cag gac cat ctt | 13623 |
| Arg Ala Tyr Met Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu |       |
| 300 305 310 315                                                 |       |
| gaa ttt tgg gag ggc gtc ttt aca ggc ctc act cat ata gat gcc cac | 13671 |
| Glu Phe Trp Glu Gly Val Phe Thr Gly Leu Thr His Ile Asp Ala His |       |
| 320 325 330                                                     |       |
| ttt cta tcc cag aca aag cag agt ggg gag aac ctt cct tac ctg gta | 13719 |
| Phe Leu Ser Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val |       |
| 335 340 345                                                     |       |
| gcg tac caa gcc acc gtg tgc gct agg gct caa gcc cct ccc cca tcg | 13767 |
| Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser |       |
| 350 355 360                                                     |       |
| tgg gac cag atg tgg aag tgt ttg att cgc ctc aag ccc acc ctc cat | 13815 |
| Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His |       |
| 365 370 375                                                     |       |
| ggg cca aca ccc ctg cta tac aga ctg ggc gct gtt cag aat gaa atc | 13863 |
| Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile |       |
| 380 385 390 395                                                 |       |
| acc ctg acg cac cca gtc acc aaa tac atc atg aca tgc atg tcg gcc | 13911 |
| Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala |       |
| 400 405 410                                                     |       |
| gac ctg gag gtc gtc acg agc acc tgg gtg ctc gtt ggc ggc gtc ctg | 13959 |
| Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu |       |
| 415 420 425                                                     |       |
| gct gct ttg gcc gcg tat tgc ctg tca aca ggc tgc gtg gtc ata gtg | 14007 |
| Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val |       |
| 430 435 440                                                     |       |
| ggc agg gtc gtc ttg tcc ggg aag ccg gca atc ata cct gac agg gaa | 14055 |
| Gly Arg Val Val Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu |       |
| 445 450 455                                                     |       |
| gtc ctc tac cga gag ttc gat gag atg gaa gag tgc tct cag cac tta | 14103 |
| Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu |       |
| 460 465 470 475                                                 |       |
| ccg tac atc gag caa ggg atg atg ctc gcc gag cag ttc aag cag aag | 14151 |
| Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys |       |
| 480 485 490                                                     |       |
| gcc ctc ggc ctc ctg cag acc gcg tcc cgt cag gca gag gtt atc gcc | 14199 |
| Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala |       |
| 495 500 505                                                     |       |
| cct gct gtc cag acc aac tgg caa aaa ctc gag acc ttc tgg gcg aag | 14247 |
| Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys |       |
| 510 515 520                                                     |       |
| cat atg tgg aac ttc atc agt ggg ata caa tac ttg gcg ggc ttg tca | 14295 |
| His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser |       |
| 525 530 535                                                     |       |

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|-----------------------------------------------------------------|-------|
| acg ctg cct ggt aac ccc gcc att gct tca ttg atg gct ttt aca gct | 14343 |
| Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala |       |
| 540 545 550 555                                                 |       |
| gct gtc acc agc cca cta acc act agc caa acc ctc ctc ttc aac ata | 14391 |
| Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile |       |
| 560 565 570                                                     |       |
| ttg ggg ggg tgg gtg gct gcc cag ctc gcc gcc ccc ggt gcc gct act | 14439 |
| Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr |       |
| 575 580 585                                                     |       |
| gcc ttt gtg ggc gct ggc tta gct ggc gcc gcc atc ggc agt gtt gga | 14487 |
| Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly |       |
| 590 595 600                                                     |       |
| ctg ggg aag gtc ctc ata gac atc ctt gca ggg tat ggc gcg ggc gtg | 14535 |
| Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val |       |
| 605 610 615                                                     |       |
| gcg gga gct ctt gtg gca ttc aag atc atg agc ggt gag gtc ccc tcc | 14583 |
| Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser |       |
| 620 625 630 635                                                 |       |
| acg gag gac ctg gtc aat cta ctg ccc gcc atc ctc tcg ccc gga gcc | 14631 |
| Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala |       |
| 640 645 650                                                     |       |
| ctc gta gtc ggc gtg gtc tgt gca gca ata ctg cgc cgg cac gtt ggc | 14679 |
| Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly |       |
| 655 660 665                                                     |       |
| ccg ggc gag ggg gca gtg cag tgg atg aac cgg ctg ata gcc ttc gcc | 14727 |
| Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala |       |
| 670 675 680                                                     |       |
| tcc cgg ggg aac cat gtt tcc ccc acg cac tac gtg ccg gag agc gat | 14775 |
| Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp |       |
| 685 690 695                                                     |       |
| gca gct gcc cgc gtc act gcc ata ctc agc agc ctc act gta acc cag | 14823 |
| Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln |       |
| 700 705 710 715                                                 |       |
| ctc ctg agg cga ctg cac cag tgg ata agc tcg gag tgt acc act cca | 14871 |
| Leu Leu Arg Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro |       |
| 720 725 730                                                     |       |
| tgc tcc ggt tcc tgg cta agg gac atc tgg gac tgg ata tgc gag gtg | 14919 |
| Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val |       |
| 735 740 745                                                     |       |
| ttg agc gac ttt aag acc tgg cta aaa gct aag ctc atg cca cag ctg | 14967 |
| Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu |       |
| 750 755 760                                                     |       |
| cct ggg atc ccc ttt gtg tcc tgc cag cgc ggg tat aag ggg gtc tgg | 15015 |
| Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp |       |
| 765 770 775                                                     |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| cga ggg gac ggc atc atg cac act cgc tgc cac tgt gga gct gag atc | 15063 |
| Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile |       |
| 780 785 790 795                                                 |       |
| act gga cat gtc aaa aac ggg acg atg agg atc gtc ggt cct agg acc | 15111 |
| Thr Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr |       |
| 800 805 810                                                     |       |
| tgc agg aac atg tgg agt ggg acc ttc ccc att aat gcc tac acc acg | 15159 |
| Cys Arg Asn Met Trp Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr |       |
| 815 820 825                                                     |       |
| ggc ccc tgt acc ccc ctt cct gcg ccg aac tac acg ttc gcg cta tgg | 15207 |
| Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp |       |
| 830 835 840                                                     |       |
| agg gtg tct gca gag gaa tac gtg gag ata agg cag gtg ggg gac ttc | 15255 |
| Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe |       |
| 845 850 855                                                     |       |
| cac tac gtg acg ggt atg act act gac aat ctt aaa tgc ccg tgc cag | 15303 |
| His Tyr Val Thr Gly Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln |       |
| 860 865 870 875                                                 |       |
| gtc cca tcg ccc gaa ttt ttc aca gaa ttg gac ggg gtg cgc cta cat | 15351 |
| Val Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His |       |
| 880 885 890                                                     |       |
| agg ttt gcg ccc ccc tgc aag ccc ttg ctg cgg gag gag gta tca ttc | 15399 |
| Arg Phe Ala Pro Pro Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe |       |
| 895 900 905                                                     |       |
| aga gta gga ctc cac gaa tac ccg gta ggg tcg caa tta cct tgc gag | 15447 |
| Arg Val Gly Leu His Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu |       |
| 910 915 920                                                     |       |
| ccc gaa ccg gac gtg gcc gtg ttg acg tcc atg ctc act gat ccc tcc | 15495 |
| Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser |       |
| 925 930 935                                                     |       |
| cat ata aca gca gag gcg gcc ggg cga agg ttg gcg agg gga tca ccc | 15543 |
| His Ile Thr Ala Glu Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro |       |
| 940 945 950 955                                                 |       |
| ccc tct gtg gcc agc tcc tcg gct agc cag cta tcc gct cca tct ctc | 15591 |
| Pro Ser Val Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu |       |
| 960 965 970                                                     |       |
| aag gca act tgc acc gct aac cat gac tcc cct gat gct gag ctc ata | 15639 |
| Lys Ala Thr Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile |       |
| 975 980 985                                                     |       |
| gag gcc aac ctc cta tgg agg cag gag atg ggc ggc aac atc acc agg | 15687 |
| Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg |       |
| 990 995 1000                                                    |       |
| gtt gag tca gaa aac aaa gtg gtg att ctg gac tcc ttc gat ccg ctt | 15735 |
| Val Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu |       |
| 1005 1010 1015                                                  |       |

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|                                                                 |       |
|-----------------------------------------------------------------|-------|
| gct aac ttg cta tcc gta gag gaa gct tgc agc ctg acg ccc cca cac | 16503 |
| Ala Asn Leu Leu Ser Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His |       |
| 1260 1265 1270 1275                                             |       |
| tca gcc aaa tcc aag ttt ggt tat ggg gca aaa gac gtc cgt tgc cat | 16551 |
| Ser Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His |       |
| 1280 1285 1290                                                  |       |
| gcc aga aag gcc gta acc cac atc aac tcc gtg tgg aaa gac ctt ctg | 16599 |
| Ala Arg Lys Ala Val Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu |       |
| 1295 1300 1305                                                  |       |
| gaa gac aat gta aca cca ata gac act acc atc atg gct aag aac gag | 16647 |
| Glu Asp Asn Val Thr Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu |       |
| 1310 1315 1320                                                  |       |
| gtt ttc tgc gtt cag cct gag aag ggg ggt cgt aag cca gct cgt ctc | 16695 |
| Val Phe Cys Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu |       |
| 1325 1330 1335                                                  |       |
| atc gtg ttc ccc gat ctg ggc gtg cgc gtg tgc gaa aag atg gct ttg | 16743 |
| Ile Val Phe Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu |       |
| 1340 1345 1350 1355                                             |       |
| tac gac gtg gtt aca aag ctc ccc ttg gcc gtg atg gga agc tcc tac | 16791 |
| Tyr Asp Val Val Thr Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr |       |
| 1360 1365 1370                                                  |       |
| gga ttc caa tac tca cca gga cag cgg gtt gaa ttc ctc gtg caa gcg | 16839 |
| Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala |       |
| 1375 1380 1385                                                  |       |
| tgg aag tcc aag aaa acc cca atg ggg ttc tcg tat gat acc cgc tgc | 16887 |
| Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys |       |
| 1390 1395 1400                                                  |       |
| ttt gac tcc aca gtc act gag agc gac atc cgt acg gag gag gca atc | 16935 |
| Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile |       |
| 1405 1410 1415                                                  |       |
| tac caa tgt tgt gac ctc gac ccc caa gcc cgc gtg gcc atc aag tcc | 16983 |
| Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser |       |
| 1420 1425 1430 1435                                             |       |
| ctc acc gag agg ctt tat gtt ggg ggc cct ctt acc aat tca agg ggg | 17031 |
| Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly |       |
| 1440 1445 1450                                                  |       |
| gag aac tgc ggc tat cgc agg tgc cgc gcg agc ggc gta ctg aca act | 17079 |
| Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr |       |
| 1455 1460 1465                                                  |       |
| agc tgt ggt aac acc ctc act tgc tac atc aag gcc cgg gca gcc tgt | 17127 |
| Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys |       |
| 1470 1475 1480                                                  |       |
| cga gcc gca ggg ctc cag gac tgc acc atg ctc gtg tgt ggc gac gac | 17175 |
| Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp |       |
| 1485 1490 1495                                                  |       |

|                                                                                    |       |
|------------------------------------------------------------------------------------|-------|
| tta gtc gtt atc tgt gaa agc gcg ggg gtc cag gag gac gcg gcg agc                    | 17223 |
| Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser                    |       |
| 1500                      1505                      1510                      1515 |       |
| ctg aga gcc ttc acg gag gct atg acc agg tac tcc gcc ccc cct ggg                    | 17271 |
| Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly                    |       |
| 1520                      1525                      1530                           |       |
| gac ccc cca caa cca gaa tac gac ttg gag ctc ata aca tca tgc tcc                    | 17319 |
| Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser                    |       |
| 1535                      1540                      1545                           |       |
| tcc aac gtg tca gtc gcc cac gac ggc gct gga aag agg gtc tac tac                    | 17367 |
| Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr                    |       |
| 1550                      1555                      1560                           |       |
| ctc acc cgt gac cct aca acc ccc ctc gcg aga gct gcg tgg gag aca                    | 17415 |
| Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr                    |       |
| 1565                      1570                      1575                           |       |
| gca aga cac act cca gtc aat tcc tgg cta ggc aac ata atc atg ttt                    | 17463 |
| Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe                    |       |
| 1580                      1585                      1590                      1595 |       |
| gcc ccc aca ctg tgg gcg agg atg ata ctg atg acc cat ttc ttt agc                    | 17511 |
| Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser                    |       |
| 1600                      1605                      1610                           |       |
| gtc ctt ata gcc agg gac cag ctt gaa cag gcc ctc gat tgc gag atc                    | 17559 |
| Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile                    |       |
| 1615                      1620                      1625                           |       |
| tac ggg gcc tgc tac tcc ata gaa cca ctg gat cta cct cca atc att                    | 17607 |
| Tyr Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile                    |       |
| 1630                      1635                      1640                           |       |
| caa aga ctc cat ggc ctc agc gca ttt tca ctc cac agt tac tct cca                    | 17655 |
| Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro                    |       |
| 1645                      1650                      1655                           |       |
| ggg gaa atc aat agg gtg gcc gca tgc ctc aga aaa ctt ggg gta ccg                    | 17703 |
| Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro                    |       |
| 1660                      1665                      1670                      1675 |       |
| ccc ttg cga gct tgg aga cac cgg gcc cgg agc gtc cgc gct agg ctt                    | 17751 |
| Pro Leu Arg Ala Trp Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu                    |       |
| 1680                      1685                      1690                           |       |
| ctg gcc aga gga ggc agg gct gcc ata tgt ggc aag tac ctc ttc aac                    | 17799 |
| Leu Ala Arg Gly Gly Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn                    |       |
| 1695                      1700                      1705                           |       |
| tgg gca gta aga aca aag ctc aaa ctc act cca ata gcg gcc gct ggc                    | 17847 |
| Trp Ala Val Arg Thr Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly                    |       |
| 1710                      1715                      1720                           |       |
| cag ctg gac ttg tcc ggc tgg ttc acg gct ggc tac agc ggg gga gac                    | 17895 |
| Gln Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp                    |       |
| 1725                      1730                      1735                           |       |



att tat cac agc gtg tct cat gcc cgg ccc cgc tgg atc tgg ttt tgc 17943  
 Ile Tyr His Ser Val Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys  
 1740 1745 1750 1755  
  
 cta ctc ctg ctt gct gca ggg gta ggc atc tac ctc ctc ccc aac cga 17991  
 Leu Leu Leu Leu Ala Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg  
 1760 1765 1770  
  
 atg agc acg aat cct aaa cct caa aga aag acc aaa cgt aac acc aac 18039  
 Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn  
 1775 1780 1785  
  
 cgg cgg cgg cag gac gtc aag ttc ccg ggt ggc ggt cag atc gtt ggt 18087  
 Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly  
 1790 1795 1800  
  
 gga gtt tac ttg ttg ccg cgc agg ggc cct aga ttg ggt gtg cgc gcg 18135  
 Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala  
 1805 1810 1815  
  
 acg aga aag act tcc gag cgg tcg caa cct cga ggt aga cgt cag cct 18183  
 Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro  
 1820 1825 1830 1835  
  
 atc ccc aag gct cgt cgg ccc gag ggc agg acc tgg gct cag ccc ggg 18231  
 Ile Pro Lys Ala Arg Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly  
 1840 1845 1850  
  
 tac cct tgg ccc ctc tat ggc aat gag ggc tgc ggg tgg gcg gga tgg 18279  
 Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp  
 1855 1860 1865  
  
 ctc ctg tct ccc cgt ggc tct cgg cct agc tgg ggc ccc aca gac ccc 18327  
 Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro  
 1870 1875 1880  
  
 cgg cgt agg tcg cgc aat ttg ggt aag gtc atc gat acc ctt acg tgc 18375  
 Arg Arg Arg Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys  
 1885 1890 1895  
  
 ggc ttc gcc gac ctc atg ggg tac ata ccg ctc gtc taatagtcga 18421  
 Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val  
 1900 1905 1910  
  
 ctttggtccc actgtacttt tagctcgtac aaaatacaat atacttttca tttctccgta 18481  
 aacaacatgt tttcccatgt aatatccttt tctatttttc gttccgttac caactttaca 18541  
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 aagatgaatg tgaatcgaat cctaagagaa ttggatctga tccacaggac ggggtgtggtc 18721  
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 aggatgacga tgagcgcat gttagatttc atacacgggt cctgactgcg ttagcaat 19021  
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 atttgtgagt ttagtatata tgcatttact tataatacag ttttttagtt ttgtggccg 19201  
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 tcccttccct ttgcaaatag tcctcttcca acaataataa tgtcagatcc ttagagagacc 19321  
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 ttgacatga tttatcttcg tttcctgcag gttttgttc tgtgcagttg ggtaagaat 20041  
 actgggcaat ttcattgttc ttcaacta catatgcgta tatatacaa tctaagtctg 20101  
 tgctccttc ttcgttcttc cttctgttcg gagattaccg aatcaaaaaa atttcaagga 20161  
 aaccgaaatc aaaaaaaga ataaaaaaa aatgatgaat tgaaaagctt atcgat 20217

<210> 17

<211> 1911

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:  
pd.delta.NS3NS5.pj.core140

<400> 17

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| Met | Ala | Ala | Tyr | Ala | Ala | Gln | Gly | Tyr | Lys | Val | Leu | Val | Leu | Asn | Pro |
| 1   |     |     |     |     |     | 5   |     |     | 10  |     |     |     |     | 15  |     |

Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His  
 20 25 30  
 Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly  
 35 40 45  
 Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly  
 50 55 60  
 Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser  
 65 70 75 80  
 Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala  
 85 90 95  
 Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro  
 100 105 110  
 Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser  
 115 120 125  
 Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val  
 130 135 140  
 Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys  
 145 150 155 160  
 Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala  
 165 170 175  
 Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val  
 180 185 190  
 Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe  
 195 200 205  
 Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe  
 210 215 220  
 Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro Gln Asp  
 225 230 235 240  
 Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro  
 245 250 255  
 Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe  
 260 265 270  
 Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr  
 275 280 285  
 Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn  
 290 295 300  
 Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly  
 305 310 315 320  
 Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr  
 325 330 335

Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln Ala Thr  
 340 345 350  
 Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp  
 355 360 365  
 Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu  
 370 375 380  
 Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile Thr Leu Thr His Pro  
 385 390 395 400  
 Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala Asp Leu Glu Val Val  
 405 410 415  
 Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala  
 420 425 430  
 Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val Gly Arg Val Val Leu  
 435 440 445  
 Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu  
 450 455 460  
 Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln  
 465 470 475 480  
 Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu  
 485 490 495  
 Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala Pro Ala Val Gln Thr  
 500 505 510  
 Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys His Met Trp Asn Phe  
 515 520 525  
 Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn  
 530 535 540  
 Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro  
 545 550 555 560  
 Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val  
 565 570 575  
 Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala  
 580 585 590  
 Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu  
 595 600 605  
 Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val  
 610 615 620  
 Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val  
 625 630 635 640  
 Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val  
 645 650 655

Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala  
 660 665 670  
 Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His  
 675 680 685  
 Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val  
 690 695 700  
 Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln Leu Leu Arg Arg Leu  
 705 710 715 720  
 His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp  
 725 730 735  
 Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys  
 740 745 750  
 Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe  
 755 760 765  
 Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile  
 770 775 780  
 Met His Thr Arg Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys  
 785 790 795 800  
 Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr Cys Arg Asn Met Trp  
 805 810 815  
 Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro  
 820 825 830  
 Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp Arg Val Ser Ala Glu  
 835 840 845  
 Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe His Tyr Val Thr Gly  
 850 855 860  
 Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln Val Pro Ser Pro Glu  
 865 870 875 880  
 Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His Arg Phe Ala Pro Pro  
 885 890 895  
 Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe Arg Val Gly Leu His  
 900 905 910  
 Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val  
 915 920 925  
 Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu  
 930 935 940  
 Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Val Ala Ser  
 945 950 955 960  
 Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr  
 965 970 975

Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile Glu Ala Asn Leu Leu  
                   980                                  985                                  990

Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn  
                   995                                  1000                                  1005

Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu Val Ala Glu Glu Asp  
                   1010                                  1015                                  1020

Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Arg Arg  
 025                                  1030                                  1035                                  1040

Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro Asp Tyr Asn Pro Pro  
                                   1045                                  1050                                  1055

Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu Pro Pro Val Val His  
                                   1060                                  1065                                  1070

Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro Val Pro Pro Pro Arg  
                   1075                                  1080                                  1085

Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr Leu Ser Thr Ala Leu  
                   1090                                  1095                                  1100

Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser Ser Thr Ser Gly Ile  
 105                                  1110                                  1115                                  1120

Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser Gly Cys  
                                   1125                                  1130                                  1135

Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu  
                   1140                                  1145                                  1150

Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val  
                   1155                                  1160                                  1165

Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys Cys Ser Met Ser Tyr  
                   1170                                  1175                                  1180

Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala Ala Glu Glu Gln Lys  
 185                                  1190                                  1195                                  1200

Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu  
                                   1205                                  1210                                  1215

Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln Arg Gln Lys Lys Val  
                   1220                                  1225                                  1230

Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His Tyr Gln Asp Val Leu  
                   1235                                  1240                                  1245

Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser  
                   1250                                  1255                                  1260

Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys  
 265                                  1270                                  1275                                  1280

Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val  
                                   1285                                  1290                                  1295

Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn Val Thr  
 1300 1305 1310  
 Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln  
 1315 1320 1325  
 Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp  
 1330 1335 1340  
 Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr  
 345 1350 1355 1360  
 Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser  
 1365 1370 1375  
 Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys  
 1380 1385 1390  
 Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val  
 1395 1400 1405  
 Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp  
 1410 1415 1420  
 Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu  
 425 1430 1435 1440  
 Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr  
 1445 1450 1455  
 Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr  
 1460 1465 1470  
 Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu  
 1475 1480 1485  
 Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys  
 1490 1495 1500  
 Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser Leu Arg Ala Phe Thr  
 505 1510 1515 1520  
 Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Gln Pro  
 1525 1530 1535  
 Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val  
 1540 1545 1550  
 Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro  
 1555 1560 1565  
 Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro  
 1570 1575 1580  
 Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe Ala Pro Thr Leu Trp  
 585 1590 1595 1600  
 Ala Arg Met Ile Leu Met Thr His Phe Phe Ser Val Leu Ile Ala Arg  
 1605 1610 1615

Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile Tyr Gly Ala Cys Tyr  
 1620 1625 1630  
 Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu His Gly  
 1635 1640 1645  
 Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg  
 1650 1655 1660  
 Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Ala Trp  
 665 1670 1675 1680  
 Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ala Arg Gly Gly  
 1685 1690 1695  
 Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr  
 1700 1705 1710  
 Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly Gln Leu Asp Leu Ser  
 1715 1720 1725  
 Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val  
 1730 1735 1740  
 Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys Leu Leu Leu Leu Ala  
 745 1750 1755 1760  
 Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg Met Ser Thr Asn Pro  
 1765 1770 1775  
 Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn Arg Arg Pro Gln Asp  
 1780 1785 1790  
 Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly Gly Val Tyr Leu Leu  
 1795 1800 1805  
 Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala Thr Arg Lys Thr Ser  
 1810 1815 1820  
 Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro Ile Pro Lys Ala Arg  
 825 1830 1835 1840  
 Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly Tyr Pro Trp Pro Leu  
 1845 1850 1855  
 Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp Leu Leu Ser Pro Arg  
 1860 1865 1870  
 Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro Arg Arg Arg Ser Arg  
 1875 1880 1885  
 Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys Gly Phe Ala Asp Leu  
 1890 1895 1900  
 Met Gly Tyr Ile Pro Leu Val  
 905 1910

&lt;210&gt; 18



&lt;211&gt; 20247

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence:

pd.delta.NS3NS5.pj.core150

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (12679) .. (18441)

&lt;400&gt; 18

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 cggatcaacg ttcttaatat cgctgaatct tccacaattg atgaaagtag ctaggaagag 180  
 gaattggtat aaagtttttg tttttgtaaa tctcgaagta tactcaaacg aatttagtat 240  
 tttctcagtg atctcccaga tgetttcacc ctacttaga agtgctttaa gcattttttt 300  
 actgtggcta tttcccttat ctgcttcttc cgatgattcg aactgtaatt gcaaactact 360  
 tacaatatca gtgatatcag attgatgttt ttgtccatag taaggaataa ttgtaaattc 420  
 ccaagcagga atcaatttct ttaatgaggc ttccagaatt gttgcttttt gcgtcttgta 480  
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 ataggttagt tcagcagcac ataatgctat tttctcacct gaaggctctt caaacctttc 660  
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 gcttagcgcc gatcttgtgt gcaattgata tctagtttca actactctat ttatcttgta 780  
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 cgttcttttcg aaaaatgcac cggccgcgca ttatttgtac tgcgaaaata attggtactg 900  
 cggtatcttc atttcatatt ttaaaaatgc acctttgctg cttttcctta attttttagac 960  
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| Thr Ser Gly Asp Val Val Val Ala Thr Asp Ala Leu Met Thr Gly     |       |
| 190 195 200                                                     |       |
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| Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr |       |
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| cag aca gtc gat ttc agc ctt gac cct acc ttc acc att gag aca atc | 13383 |
| Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile |       |
| 220 225 230 235                                                 |       |
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| 240 245 250                                                     |       |
| ggc agg ggg aag cca ggc atc tac aga ttt gtg gca ccg ggg gag cgc | 13479 |
| Gly Arg Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg |       |
| 255 260 265                                                     |       |
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| Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala |       |
| 270 275 280                                                     |       |
| ggc tgt gct tgg tat gag ctc acg ccc gcc gag act aca gtt agg cta | 13575 |
| Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu |       |
| 285 290 295                                                     |       |
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| Arg Ala Tyr Met Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu |       |
| 300 305 310 315                                                 |       |
| gaa ttt tgg gag ggc gtc ttt aca ggc ctc act cat ata gat gcc cac | 13671 |
| Glu Phe Trp Glu Gly Val Phe Thr Gly Leu Thr His Ile Asp Ala His |       |
| 320 325 330                                                     |       |
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| Phe Leu Ser Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val |       |
| 335 340 345                                                     |       |
| gcg tac caa gcc acc gtg tgc gct agg gct caa gcc cct ccc cca tcg | 13767 |
| Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser |       |
| 350 355 360                                                     |       |
| tgg gac cag atg tgg aag tgt ttg att cgc ctc aag ccc acc ctc cat | 13815 |
| Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His |       |
| 365 370 375                                                     |       |
| ggg cca aca ccc ctg cta tac aga ctg ggc gct gtt cag aat gaa atc | 13863 |
| Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile |       |
| 380 385 390 395                                                 |       |
| acc ctg acg cac cca gtc acc aaa tac atc atg aca tgc atg tcg gcc | 13911 |
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| 400 405 410                                                     |       |

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| Ala Ala Leu Ala Ala Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val |       |
| 430 435 440                                                     |       |
| ggc agg gtc gtc ttg tcc ggg aag ccg gca atc ata cct gac agg gaa | 14055 |
| Gly Arg Val Val Leu Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu |       |
| 445 450 455                                                     |       |
| gtc ctc tac cga gag ttc gat gag atg gaa gag tgc tct cag cac tta | 14103 |
| Val Leu Tyr Arg Glu Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu |       |
| 460 465 470 475                                                 |       |
| ccg tac atc gag caa ggg atg atg ctc gcc gag cag ttc aag cag aag | 14151 |
| Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys |       |
| 480 485 490                                                     |       |
| gcc ctc ggc ctc ctg cag acc gcg tcc cgt cag gca gag gtt atc gcc | 14199 |
| Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala |       |
| 495 500 505                                                     |       |
| cct gct gtc cag acc aac tgg caa aaa ctc gag acc ttc tgg gcg aag | 14247 |
| Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys |       |
| 510 515 520                                                     |       |
| cat atg tgg aac ttc atc agt ggg ata caa tac ttg gcg ggc ttg tca | 14295 |
| His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser |       |
| 525 530 535                                                     |       |
| acg ctg cct ggt aac ccc gcc att gct tca ttg atg gct ttt aca gct | 14343 |
| Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala |       |
| 540 545 550 555                                                 |       |
| gct gtc acc agc cca cta acc act agc caa acc ctc ctc ttc aac ata | 14391 |
| Ala Val Thr Ser Pro Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile |       |
| 560 565 570                                                     |       |
| ttg ggg ggg tgg gtg gct gcc cag ctc gcc gcc ccc ggt gcc gct act | 14439 |
| Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr |       |
| 575 580 585                                                     |       |
| gcc ttt gtg ggc gct ggc tta gct ggc gcc gcc atc ggc agt gtt gga | 14487 |
| Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly |       |
| 590 595 600                                                     |       |
| ctg ggg aag gtc ctc ata gac atc ctt gca ggg tat ggc gcg ggc gtg | 14535 |
| Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val |       |
| 605 610 615                                                     |       |
| gcg gga gct ctt gtg gca ttc aag atc atg agc ggt gag gtc ccc tcc | 14583 |
| Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser |       |
| 620 625 630 635                                                 |       |
| acg gag gac ctg gtc aat cta ctg ccc gcc atc ctc tcg ccc gga gcc | 14631 |
| Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala |       |
| 640 645 650                                                     |       |

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|-----------------------------------------------------------------|-------|
| ctc gta gtc ggc gtg gtc tgt gca gca ata ctg cgc cgg cac gtt ggc | 14679 |
| Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly |       |
| 655 660 665                                                     |       |
| ccg ggc gag ggg gca gtg cag tgg atg aac cgg ctg ata gcc ttc gcc | 14727 |
| Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala |       |
| 670 675 680                                                     |       |
| tcc cgg ggg aac cat gtt tcc ccc acg cac tac gtg ccg gag agc gat | 14775 |
| Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp |       |
| 685 690 695                                                     |       |
| gca gct gcc cgc gtc act gcc ata ctc agc agc ctc act gta acc cag | 14823 |
| Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln |       |
| 700 705 710 715                                                 |       |
| ctc ctg agg cga ctg cac cag tgg ata agc tcg gag tgt acc act cca | 14871 |
| Leu Leu Arg Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro |       |
| 720 725 730                                                     |       |
| tgc tcc ggt tcc tgg cta agg gac atc tgg gac tgg ata tgc gag gtg | 14919 |
| Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val |       |
| 735 740 745                                                     |       |
| ttg agc gac ttt aag acc tgg cta aaa gct aag ctc atg cca cag ctg | 14967 |
| Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu |       |
| 750 755 760                                                     |       |
| cct ggg atc ccc ttt gtg tcc tgc cag cgc ggg tat aag ggg gtc tgg | 15015 |
| Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp |       |
| 765 770 775                                                     |       |
| cga ggg gac ggc atc atg cac act cgc tgc cac tgt gga gct gag atc | 15063 |
| Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile |       |
| 780 785 790 795                                                 |       |
| act gga cat gtc aaa aac ggg acg atg agg atc gtc ggt cct agg acc | 15111 |
| Thr Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr |       |
| 800 805 810                                                     |       |
| tgc agg aac atg tgg agt ggg acc ttc ccc att aat gcc tac acc acg | 15159 |
| Cys Arg Asn Met Trp Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr |       |
| 815 820 825                                                     |       |
| ggc ccc tgt acc ccc ctt cct gcg ccg aac tac acg ttc gcg cta tgg | 15207 |
| Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp |       |
| 830 835 840                                                     |       |
| agg gtg tct gca gag gaa tac gtg gag ata agg cag gtg ggg gac ttc | 15255 |
| Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe |       |
| 845 850 855                                                     |       |
| cac tac gtg acg ggt atg act act gac aat ctt aaa tgc ccg tgc cag | 15303 |
| His Tyr Val Thr Gly Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln |       |
| 860 865 870 875                                                 |       |
| gtc cca tcg ccc gaa ttt ttc aca gaa ttg gac ggg gtg cgc cta cat | 15351 |
| Val Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His |       |
| 880 885 890                                                     |       |

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|-----------------------------------------------------------------|-------|
| agg ttt gcg ccc ccc tgc aag ccc ttg ctg cgg gag gag gta tca ttc | 15399 |
| Arg Phe Ala Pro Pro Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe |       |
| 895 900 905                                                     |       |
| aga gta gga ctc cac gaa tac ccg gta ggg tcg caa tta cct tgc gag | 15447 |
| Arg Val Gly Leu His Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu |       |
| 910 915 920                                                     |       |
| ccc gaa ccg gac gtg gcc gtg ttg acg tcc atg ctc act gat ccc tcc | 15495 |
| Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser |       |
| 925 930 935                                                     |       |
| cat ata aca gca gag gcg gcc ggg cga agg ttg gcg agg gga tca ccc | 15543 |
| His Ile Thr Ala Glu Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro |       |
| 940 945 950 955                                                 |       |
| ccc tct gtg gcc agc tcc tcg gct agc cag cta tcc gct cca tct ctc | 15591 |
| Pro Ser Val Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu |       |
| 960 965 970                                                     |       |
| aag gca act tgc acc gct aac cat gac tcc cct gat gct gag ctc ata | 15639 |
| Lys Ala Thr Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile |       |
| 975 980 985                                                     |       |
| gag gcc aac ctc cta tgg agg cag gag atg ggc ggc aac atc acc agg | 15687 |
| Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg |       |
| 990 995 1000                                                    |       |
| gtt gag tca gaa aac aaa gtg gtg att ctg gac tcc ttc gat ccg ctt | 15735 |
| Val Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu |       |
| 1005 1010 1015                                                  |       |
| gtg gcg gag gag gac gag ccg gag atc tcc gta ccc gca gaa atc ctg | 15783 |
| Val Ala Glu Glu Asp Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu |       |
| 1020 1025 1030 1035                                             |       |
| cgg aag tct ccg aga ttc gcc cag gcc ctg ccc gtt tgg gcg ccg ccg | 15831 |
| Arg Lys Ser Arg Arg Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro |       |
| 1040 1045 1050                                                  |       |
| gac tat aac ccc ccg cta gtg gag acg tgg aaa aag ccc gac tac gaa | 15879 |
| Asp Tyr Asn Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu |       |
| 1055 1060 1065                                                  |       |
| cca cct gtg gtc cat ggc tgc ccg ctt cca cct cca aag tcc cct cct | 15927 |
| Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro |       |
| 1070 1075 1080                                                  |       |
| gtg cct ccg cct ccg aag aag ccg acg gtg gtc ctc act gaa tca acc | 15975 |
| Val Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr |       |
| 1085 1090 1095                                                  |       |
| cta tct act gcc ttg gcc gag ctc gcc acc aga agc ttt ggc agc tcc | 16023 |
| Leu Ser Thr Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser |       |
| 1100 1105 1110 1115                                             |       |
| tca act tcc ggc att acg ggc gac aat acg aca aca tcc tct gag ccc | 16071 |
| Ser Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro |       |
| 1120 1125 1130                                                  |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| gcc cct tct ggc tgc ccc ccc gac tcc gac gct gag tcc tat tcc tcc | 16119 |
| Ala Pro Ser Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser |       |
| 1135 1140 1145                                                  |       |
| atg ccc ccc ctg gag ggg gag cct ggg gat ccg gat ctt agc gac ggg | 16167 |
| Met Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly |       |
| 1150 1155 1160                                                  |       |
| tca tgg tca acg gtc agt agt gag gcc aac gcg gag gat gtc gtg tgc | 16215 |
| Ser Trp Ser Thr Val Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys |       |
| 1165 1170 1175                                                  |       |
| tgc tca atg tct tac tct tgg aca ggc gca ctc gtc acc ccg tgc gcc | 16263 |
| Cys Ser Met Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala |       |
| 1180 1185 1190 1195                                             |       |
| gcg gaa gaa cag aaa ctg ccc atc aat gca cta agc aac tcg ttg cta | 16311 |
| Ala Glu Glu Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu |       |
| 1200 1205 1210                                                  |       |
| cgt cac cac aat ttg gtg tat tcc acc acc tca cgc agt gct tgc caa | 16359 |
| Arg His His Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln |       |
| 1215 1220 1225                                                  |       |
| agg cag aag aaa gtc aca ttt gac aga ctg caa gtt ctg gac agc cat | 16407 |
| Arg Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His |       |
| 1230 1235 1240                                                  |       |
| tac cag gac gta ctc aag gag gtt aaa gca gcg gcg tca aaa gtg aag | 16455 |
| Tyr Gln Asp Val Leu Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys |       |
| 1245 1250 1255                                                  |       |
| gct aac ttg cta tcc gta gag gaa gct tgc agc ctg acg ccc cca cac | 16503 |
| Ala Asn Leu Leu Ser Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His |       |
| 1260 1265 1270 1275                                             |       |
| tca gcc aaa tcc aag ttt ggt tat ggg gca aaa gac gtc cgt tgc cat | 16551 |
| Ser Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His |       |
| 1280 1285 1290                                                  |       |
| gcc aga aag gcc gta acc cac atc aac tcc gtg tgg aaa gac ctt ctg | 16599 |
| Ala Arg Lys Ala Val Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu |       |
| 1295 1300 1305                                                  |       |
| gaa gac aat gta aca cca ata gac act acc atc atg gct aag aac gag | 16647 |
| Glu Asp Asn Val Thr Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu |       |
| 1310 1315 1320                                                  |       |
| gtt ttc tgc gtt cag cct gag aag ggg ggt cgt aag cca gct cgt ctc | 16695 |
| Val Phe Cys Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu |       |
| 1325 1330 1335                                                  |       |
| atc gtg ttc ccc gat ctg ggc gtg cgc gtg tgc gaa aag atg gct ttg | 16743 |
| Ile Val Phe Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu |       |
| 1340 1345 1350 1355                                             |       |
| tac gac gtg gtt aca aag ctc ccc ttg gcc gtg atg gga agc tcc tac | 16791 |
| Tyr Asp Val Val Thr Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr |       |
| 1360 1365 1370                                                  |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| gga ttc caa tac tca cca gga cag cgg gtt gaa ttc ctc gtg caa gcg | 16839 |
| Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala |       |
| 1375 1380 1385                                                  |       |
| tgg aag tcc aag aaa acc cca atg ggg ttc tcg tat gat acc cgc tgc | 16887 |
| Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys |       |
| 1390 1395 1400                                                  |       |
| ttt gac tcc aca gtc act gag agc gac atc cgt acg gag gag gca atc | 16935 |
| Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile |       |
| 1405 1410 1415                                                  |       |
| tac caa tgt tgt gac ctc gac ccc caa gcc cgc gtg gcc atc aag tcc | 16983 |
| Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser |       |
| 1420 1425 1430 1435                                             |       |
| ctc acc gag agg ctt tat gtt ggg ggc cct ctt acc aat tca agg ggg | 17031 |
| Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly |       |
| 1440 1445 1450                                                  |       |
| gag aac tgc ggc tat cgc agg tgc cgc gcg agc ggc gta ctg aca act | 17079 |
| Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr |       |
| 1455 1460 1465                                                  |       |
| agc tgt ggt aac acc ctc act tgc tac atc aag gcc cgg gca gcc tgt | 17127 |
| Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys |       |
| 1470 1475 1480                                                  |       |
| cga gcc gca ggg ctc cag gac tgc acc atg ctc gtg tgt ggc gac gac | 17175 |
| Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp |       |
| 1485 1490 1495                                                  |       |
| tta gtc gtt atc tgt gaa agc gcg ggg gtc cag gag gac gcg gcg agc | 17223 |
| Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser |       |
| 1500 1505 1510 1515                                             |       |
| ctg aga gcc ttc acg gag gct atg acc agg tac tcc gcc ccc cct ggg | 17271 |
| Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly |       |
| 1520 1525 1530                                                  |       |
| gac ccc cca caa cca gaa tac gac ttg gag ctc ata aca tca tgc tcc | 17319 |
| Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser |       |
| 1535 1540 1545                                                  |       |
| tcc aac gtg tca gtc gcc cac gac ggc gct gga aag agg gtc tac tac | 17367 |
| Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr |       |
| 1550 1555 1560                                                  |       |
| ctc acc cgt gac cct aca acc ccc ctc gcg aga gct gcg tgg gag aca | 17415 |
| Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr |       |
| 1565 1570 1575                                                  |       |
| gca aga cac act cca gtc aat tcc tgg cta ggc aac ata atc atg ttt | 17463 |
| Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe |       |
| 1580 1585 1590 1595                                             |       |
| gcc ccc aca ctg tgg gcg agg atg ata ctg atg acc cat ttc ttt agc | 17511 |
| Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser |       |
| 1600 1605 1610                                                  |       |

|                                                                 |       |
|-----------------------------------------------------------------|-------|
| gtc ctt ata gcc agg gac cag ctt gaa cag gcc ctc gat tgc gag atc | 17559 |
| Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile |       |
| 1615 1620 1625                                                  |       |
| tac ggg gcc tgc tac tcc ata gaa cca ctg gat cta cct cca atc att | 17607 |
| Tyr Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile |       |
| 1630 1635 1640                                                  |       |
| caa aga ctc cat ggc ctc agc gca ttt tca ctc cac agt tac tct cca | 17655 |
| Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro |       |
| 1645 1650 1655                                                  |       |
| ggg gaa atc aat agg gtg gcc gca tgc ctc aga aaa ctt ggg gta ccg | 17703 |
| Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro |       |
| 1660 1665 1670 1675                                             |       |
| ccc ttg cga gct tgg aga cac cgg gcc cgg agc gtc cgc gct agg ctt | 17751 |
| Pro Leu Arg Ala Trp Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu |       |
| 1680 1685 1690                                                  |       |
| ctg gcc aga gga ggc agg gct gcc ata tgt ggc aag tac ctc ttc aac | 17799 |
| Leu Ala Arg Gly Gly Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn |       |
| 1695 1700 1705                                                  |       |
| tgg gca gta aga aca aag ctc aaa ctc act cca ata gcg gcc gct ggc | 17847 |
| Trp Ala Val Arg Thr Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly |       |
| 1710 1715 1720                                                  |       |
| cag ctg gac ttg tcc ggc tgg ttc acg gct ggc tac agc ggg gga gac | 17895 |
| Gln Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp |       |
| 1725 1730 1735                                                  |       |
| att tat cac agc gtg tct cat gcc cgg ccc cgc tgg atc tgg ttt tgc | 17943 |
| Ile Tyr His Ser Val Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys |       |
| 1740 1745 1750 1755                                             |       |
| cta ctc ctg ctt gct gca ggg gta ggc atc tac ctc ctc ccc aac cga | 17991 |
| Leu Leu Leu Leu Ala Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg |       |
| 1760 1765 1770                                                  |       |
| atg agc acg aat cct aaa cct caa aga aag acc aaa cgt aac acc aac | 18039 |
| Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn |       |
| 1775 1780 1785                                                  |       |
| cgg cgg ccg cag gac gtc aag ttc ccg ggt ggc ggt cag atc gtt ggt | 18087 |
| Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly |       |
| 1790 1795 1800                                                  |       |
| gga gtt tac ttg ttg ccg cgc agg ggc cct aga ttg ggt gtg cgc gcg | 18135 |
| Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala |       |
| 1805 1810 1815                                                  |       |
| acg aga aag act tcc gag cgg tcg caa cct cga ggt aga cgt cag cct | 18183 |
| Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro |       |
| 1820 1825 1830 1835                                             |       |
| atc ccc aag gct cgt cgg ccc gag ggc agg acc tgg gct cag ccc ggg | 18231 |
| Ile Pro Lys Ala Arg Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly |       |
| 1840 1845 1850                                                  |       |

tac cct tgg ccc ctc tat ggc aat gag ggc tgc ggg tgg gcg gga tgg 18279  
 Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp  
 1855 1860 1865

ctc ctg tct ccc cgt ggc tct cgg cct agc tgg ggc ccc aca gac ccc 18327  
 Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro  
 1870 1875 1880

cgg cgt agg tgc cgc aat ttg ggt aag gtc atc gat acc ctt acg tgc 18375  
 Arg Arg Arg Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys  
 1885 1890 1895

ggc ttc gcc gac ctc atg ggg tac ata ccg ctc gtc ggc gcc cct ctt 18423  
 Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu  
 1900 1905 1910 1915

gga ggc gct gcc agg gcc taatagtcga ctttgttccc actgtacttt 18471  
 Gly Gly Ala Ala Arg Ala  
 1920

tagctcgtac aaaatacaat atacttttca tttctccgta aacaacatgt tttcccatgt 18531  
 aatatccttt tctatattttc gttccgttac caactttaca catactttat atagctattc 18591  
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 gttataaatt cctataattt atcctattag tagctaaaaa aagatgaatg tgaatcgaat 18711  
 cctaagagaa ttggatctga tccacaggac ggggtgtggtc gccatgatcg cgtagtcgat 18771  
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 tgcatttact tataatacag ttttttagtt ttgctggcgg catcttctca aatatgcttc 19251  
 ccagcctgct tttctgtaac gttcaccttc taccttagca tcccttcctt ttgcaaatag 19311  
 tcctcttcca acaataataa tgtcagatcc tgtagagacc acatcatcca cggttctata 19371  
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 atcgtaacct tcatctcttc caccatgtc tctttgagca ataaagccga taacaaaatc 19491  
 tttgtcgctc ttgcgaatgt caacagtacc cttagtatat tctccagtag ataggagacc 19551  
 cttgcatgac aattctgcta acatcaaaag gcctctaggt tcctttgtta cttcttctgc 19611  
 cgctgcttc aaaccgctaa caatacctgg gccaccaca ccgtgtgcat tcgtaatgtc 19671



tgccattct gctattctgt atacaccgc agagtactgc aatttgactg tattaccaat 19731  
 gtcagcaaat tttctgtctt cgaagagtaa aaaattgtac ttggcggata atgccttttag 19791  
 cggettaact gtgccctcca tggaaaaatc agtcaagata tccacatgtg ttttttagtaa 19851  
 acaaattttg ggacctaatg cttcaactaa ctccagtaat tccttggtgg tacgaacatc 19911  
 caatgaagca cacaagtttg tttgcttttc gtgcatgata ttaaatagct tggcagcaac 19971  
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 ttcaacacta catatgcgta tatataccaa tctaagtctg tgctccttcc ttcgttcttc 20151  
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 ataaaaaaaa aatgatgaat tgaaaagctt atcgat 20247

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<211> 1921

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:  
 pd.delta.NS3NS5.pj.core150

<400> 19

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Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His  
 20 25 30

Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly  
 35 40 45

Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly  
 50 55 60

Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser  
 65 70 75 80

Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala  
 85 90 95

Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro  
 100 105 110

Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser  
 115 120 125

Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val  
 130 135 140

Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys

|                 |                                                 |                             |     |     |     |     |
|-----------------|-------------------------------------------------|-----------------------------|-----|-----|-----|-----|
| 145             |                                                 | 150                         |     | 155 |     | 160 |
| Asp Glu Leu Ala | Ala Lys Leu Val Ala                             | Leu Gly Ile Asn Ala Val Ala |     |     |     |     |
|                 | 165                                             |                             | 170 |     | 175 |     |
| Tyr Tyr Arg Gly | Leu Asp Val Ser Val                             | Ile Pro Thr Ser Gly Asp Val |     |     |     |     |
|                 | 180                                             |                             | 185 |     | 190 |     |
| Val Val Val Ala | Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe |                             |     |     |     |     |
|                 | 195                                             |                             | 200 |     | 205 |     |
| Asp Ser Val Ile | Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe |                             |     |     |     |     |
|                 | 210                                             |                             | 215 |     | 220 |     |
| Ser Leu Asp Pro | Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro Gln Asp |                             |     |     |     |     |
|                 | 225                                             |                             | 230 |     | 235 | 240 |
| Ala Val Ser Arg | Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro |                             |     |     |     |     |
|                 | 245                                             |                             | 250 |     | 255 |     |
| Gly Ile Tyr Arg | Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe |                             |     |     |     |     |
|                 | 260                                             |                             | 265 |     | 270 |     |
| Asp Ser Ser Val | Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr |                             |     |     |     |     |
|                 | 275                                             |                             | 280 |     | 285 |     |
| Glu Leu Thr Pro | Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn |                             |     |     |     |     |
|                 | 290                                             |                             | 295 |     | 300 |     |
| Thr Pro Gly Leu | Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly |                             |     |     |     |     |
|                 | 305                                             |                             | 310 |     | 315 | 320 |
| Val Phe Thr Gly | Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr |                             |     |     |     |     |
|                 | 325                                             |                             | 330 |     | 335 |     |
| Lys Gln Ser Gly | Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln Ala Thr |                             |     |     |     |     |
|                 | 340                                             |                             | 345 |     | 350 |     |
| Val Cys Ala Arg | Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp |                             |     |     |     |     |
|                 | 355                                             |                             | 360 |     | 365 |     |
| Lys Cys Leu Ile | Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu |                             |     |     |     |     |
|                 | 370                                             |                             | 375 |     | 380 |     |
| Leu Tyr Arg Leu | Gly Ala Val Gln Asn Glu Ile Thr Leu Thr His Pro |                             |     |     |     |     |
|                 | 385                                             |                             | 390 |     | 395 | 400 |
| Val Thr Lys Tyr | Ile Met Thr Cys Met Ser Ala Asp Leu Glu Val Val |                             |     |     |     |     |
|                 | 405                                             |                             | 410 |     | 415 |     |
| Thr Ser Thr Trp | Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala |                             |     |     |     |     |
|                 | 420                                             |                             | 425 |     | 430 |     |
| Tyr Cys Leu Ser | Thr Gly Cys Val Val Ile Val Gly Arg Val Val Leu |                             |     |     |     |     |
|                 | 435                                             |                             | 440 |     | 445 |     |
| Ser Gly Lys Pro | Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu |                             |     |     |     |     |
|                 | 450                                             |                             | 455 |     | 460 |     |

Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln  
 465 470 475 480  
 Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu  
 485 490 495  
 Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala Pro Ala Val Gln Thr  
 500 505 510  
 Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys His Met Trp Asn Phe  
 515 520 525  
 Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn  
 530 535 540  
 Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro  
 545 550 555 560  
 Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val  
 565 570 575  
 Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala  
 580 585 590  
 Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu  
 595 600 605  
 Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val  
 610 615 620  
 Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val  
 625 630 635 640  
 Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val  
 645 650 655  
 Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala  
 660 665 670  
 Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His  
 675 680 685  
 Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val  
 690 695 700  
 Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln Leu Leu Arg Arg Leu  
 705 710 715 720  
 His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp  
 725 730 735  
 Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys  
 740 745 750  
 Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe  
 755 760 765  
 Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile  
 770 775 780

Met His Thr Arg Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys  
 785 790 795 800  
 Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr Cys Arg Asn Met Trp  
 805 810 815  
 Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro  
 820 825 830  
 Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp Arg Val Ser Ala Glu  
 835 840 845  
 Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe His Tyr Val Thr Gly  
 850 855 860  
 Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln Val Pro Ser Pro Glu  
 865 870 875 880  
 Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His Arg Phe Ala Pro Pro  
 885 890 895  
 Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe Arg Val Gly Leu His  
 900 905 910  
 Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val  
 915 920 925  
 Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu  
 930 935 940  
 Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Val Ala Ser  
 945 950 955 960  
 Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr  
 965 970 975  
 Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile Glu Ala Asn Leu Leu  
 980 985 990  
 Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn  
 995 1000 1005  
 Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu Val Ala Glu Glu Asp  
 1010 1015 1020  
 Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Arg Arg  
 1025 1030 1035 1040  
 Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro Asp Tyr Asn Pro Pro  
 1045 1050 1055  
 Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu Pro Pro Val Val His  
 1060 1065 1070  
 Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro Val Pro Pro Arg  
 1075 1080 1085  
 Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr Leu Ser Thr Ala Leu  
 1090 1095 1100

Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser Ser Thr Ser Gly Ile  
 105 1110 1115 1120  
 Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser Gly Cys  
 1125 1130 1135  
 Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu  
 1140 1145 1150  
 Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val  
 1155 1160 1165  
 Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys Cys Ser Met Ser Tyr  
 1170 1175 1180  
 Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala Ala Glu Glu Gln Lys  
 185 1190 1195 1200  
 Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu  
 1205 1210 1215  
 Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln Arg Gln Lys Lys Val  
 1220 1225 1230  
 Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His Tyr Gln Asp Val Leu  
 1235 1240 1245  
 Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser  
 1250 1255 1260  
 Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys  
 265 1270 1275 1280  
 Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val  
 1285 1290 1295  
 Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn Val Thr  
 1300 1305 1310  
 Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln  
 1315 1320 1325  
 Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp  
 1330 1335 1340  
 Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr  
 345 1350 1355 1360  
 Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser  
 1365 1370 1375  
 Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys  
 1380 1385 1390  
 Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val  
 1395 1400 1405  
 Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp  
 1410 1415 1420

Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu  
 425 1430 1435 1440  
 Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr  
 1445 1450 1455  
 Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr  
 1460 1465 1470  
 Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu  
 1475 1480 1485  
 Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys  
 1490 1495 1500  
 Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser Leu Arg Ala Phe Thr  
 505 1510 1515 1520  
 Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Gln Pro  
 1525 1530 1535  
 Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val  
 1540 1545 1550  
 Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro  
 1555 1560 1565  
 Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro  
 1570 1575 1580  
 Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe Ala Pro Thr Leu Trp  
 585 1590 1595 1600  
 Ala Arg Met Ile Leu Met Thr His Phe Phe Ser Val Leu Ile Ala Arg  
 1605 1610 1615  
 Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile Tyr Gly Ala Cys Tyr  
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 Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu His Gly  
 1635 1640 1645  
 Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg  
 1650 1655 1660  
 Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Ala Trp  
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 Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ala Arg Gly Gly  
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 Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr  
 1700 1705 1710  
 Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly Gln Leu Asp Leu Ser  
 1715 1720 1725  
 Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val  
 1730 1735 1740

Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys Leu Leu Leu Leu Ala  
 745 1750 1755 1760  
 Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg Met Ser Thr Asn Pro  
 1765 1770 1775  
 Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn Arg Arg Pro Gln Asp  
 1780 1785 1790  
 Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly Gly Val Tyr Leu Leu  
 1795 1800 1805  
 Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala Thr Arg Lys Thr Ser  
 1810 1815 1820  
 Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro Ile Pro Lys Ala Arg  
 825 1830 1835 1840  
 Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly Tyr Pro Trp Pro Leu  
 1845 1850 1855  
 Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp Leu Leu Ser Pro Arg  
 1860 1865 1870  
 Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro Arg Arg Arg Ser Arg  
 1875 1880 1885  
 Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys Gly Phe Ala Asp Leu  
 1890 1895 1900  
 Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu Gly Gly Ala Ala Arg  
 905 1910 1915 1920  
 Ala